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SOME NEWER ASPECTS OF THE BIOLOGY OF INFECTIOUS MONONUCLEOSIS

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THE purpose of this communication is to discuss certain points in the natural history of a disease with protean manifestations, i.e., infectious mononucleosis. We desire to present the following aspects:

1. An allergic background was observed in all of our cases.

2. Many of the patients presented a relative paucity of granulocytes in the blood, and developed a severe sore throat. Penicillin therapy tided these individuals over until the granulocytes increased.

3. Many of the patients presented evidence of liver damage (hepatitis). This type of hepatitis improved very well with choline or methionine, in direct contradistinction to other types of hepatitis, which do not respond.

4. When Aureomycin became available, we instituted treatment with this antibiotic and noted a rather dramatic response, with subsidence of fever and decrease in size of the glands and spleen.

THE ALLERGIC BACKGROUND

We first noted in 1946 that our patients with infectious mononucleosis had an allergic family history or had classical allergy themselves.[14] The disease was interpreted as a virus infection in an individual that reacted in a special way, i.e., with the lymphatic system as the shock organ. This concept had a very special value at that time, because even if we had no way of attacking the virus, we might be able to slightly alter the substrate with antihistaminic drugs and thus help abort the infection. We have now studied fifty patients,* and in all of these we found an allergic background on careful questioning. One of us[14] reported this finding in 1946, and

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*Dr. Max Blonstein allowed us to include some of his patients, which were studied along similar lines.

received diverse reactions from competent students of this condition. One authority[20] with a large experience stated that aside from the obvious similarity between serum sickness and infectious mononucleosis (swelling of lymph nodes, lymphocytosis, fever, presence of heterophile antibodies) there was no connection between allergy and the disease under discussion. On the other hand, another internist[19] stated with equal emphasis that he had never seen a patient with infectious mononucleosis who did not have a definite history of allergy. He stated that the episodes of infectious mononucleosis often occurred within a few days following an exacerbation of either asthma or hay fever.

There have been suggestions in the literature that abnormal blood findings suggestive of infectious mononucleosis might be found in cases with clinical allergy. This was noted repeatedly by Randolph and his associates.[15-17] However, they maintained that these cases were not infectious mononucleosis, but were really evidence of "allergic toxemia," due to eating food to which the individual was allergic. Many of their patients had glandular enlargement, fatigue, deep generalized aching, atypical lymphocytes in the blood smear, but negative heterophile antibody tests. It is now conceded that a negative heterophile antibody reaction is not necessarily evidence against infectious mononucleosis.

The concept of an allergic substrate has importance both in diagnosis and treatment. An individual with a past history of allergy, and presenting fever, generalized adenopathy, and sore throat, should have infectious mononucleosis included in the differential diagnosis of his illness and should have the requisite tests done. Before the advent of Aureomycin, our treatment consisted of one of the antihistaminic drugs (Pyribenzamine, Benadryl, Trimeton, 25 mg every four hours) and aspirin 0.3 gram every four hours. This very often caused a dramatic subsidence of the condition in several days. We have recently used this treatment also in two patients who could not tolerate Aureomycin because of severe nausea and vomiting.

Ravenna and Snyder[18] recently noted that about 50 per cent of their patients with infectious mononucleosis had edema of the pharynx, soft palate, and uvula. They felt that finding this diffuse edema in the absence of exudate was a valuable sign for the presumptive clinical diagnosis of infectious mononucleosis. They had one case in which the edema extended into the larynx. This edema might suggest an allergic mechanism at work. There is also a report of a death due to laryngeal edema in infectious mononucleosis.[6] With an allergic concept in mind, anti-allergic medications can be used.

A rash often accompanies infectious mononucleosis. While this type of rash at times simulates that seen in German measles, we noted that many of our cases presented recurrent urticarial lesions at some point in their illness. This type of rash responded very well to antihistaminic drugs.

TABLE I. H. R. CASE 4. HEMATOLOGY TABLE

Date	Cytology	W.B.C.	Polymorphonuclear	Stabs	Juveniles	Large Lymphocytes	Small Lymphocytes	Monocytes	Eosinophiles	Basophiles
1/25/49	Downey+	5,600	27%	9%	4%	19%	36%	5%	—	—
1/27/49	Downey+	9,200	26%	8%	—	14%	43%	8%	1%	—
1/29/49	Downey+	11,100	25%	4%	—	17%	45%	8%	1%	—
1/31/49	Downey+	10,400	19%	6%	—	26%	40%	6%	2%	1%
2/3/49	Downey+	9,400	32%	3%	—	10%	47%	6%	2%	—
2/7/49	Downey—	8,600	34%	6%	1%	6%	44%	6%	3%	—
2/10/49	Downey—	6,300	37%	1%	—	3%	52%	3%	4%	—

TABLE II. J. G. CASE 7. HEMATOLOGY TABLE.

Date	Cytology	W.B.C.	Polymorphonuclear	Stabs	Juveniles	Large Lymphocytes	Small Lymphocytes	Monocytes	Eosinophiles	Basophiles
4/12/49	Downey+	11,700	26%	4%	0%	16%	50%	4%	0	0
4/18/49	Downey+	10,400	22%	1%	0%	15%	58%	3%	1%	0
4/23/49	No Downey	8,00	42%	4%		0	40%	9%	5%	0

GRANULOCYTOPENIC REACTION

Sore throat is so frequently seen as part of the picture of infectious mononucleosis that it must be considered one of the symptoms. This refers to the initial sore throat which is seen at the onset of the disease. This often improves, but there frequently develops later a severe ulcerative pharyngitis or acute tonsillitis. Joyce,[11] like Bernstein,[2] believes that the ulcerative pharyngitis and acute tonsillitis are complications of the disease, rather than part of the disease itself, and that the lesions are similar to complications occurring in agranulocytosis. In our cases, the development of a severe pharyngitis could almost always be forecast if the polynuclear cells were relatively few in number (Table I & II). It is true, however, that the degree of severity of the ulcerative pharyngitis could not be exactly foretold by the actual percentage of granulocytes in the peripheral blood. Since a granulocytopenia occurs in nearly every case of infectious mononucleosis, it would be attractive to believe that it was responsible for the lowered resistance to secondary infection of the individual. This, as has been stated, is only generally true.

In the foregoing discussion, we have stressed that a relative, rather than an absolute, granulocytopenia was present during the phase of ulcerative pharyngitis. For example, in one of Joyce's cases the white blood count was 21,050 with 39 per cent neutrophiles, making an actual count of 8,209 neutrophiles per cubic millimeter of blood. Certainly the absolute number of polynuclear neutrophiles is even higher than would be present normally, even though the relative proportion is lower. This finding could be correlated with the development of ulcerative pharyngitis only if there was a mutual antagonism between polynuclear neutrophiles and lymphocytes which would make the force of 8,209 neutrophiles less effective as

guardians against secondary infection than they would otherwise be. This very concept has been noted and discussed by Crosfill.[5]

Other work along the same line is the observation that an impure substance extracted from the urine of patients with myelocytic leukemia may temporarily retard the progress of lymphatic leukemia. These observers found that the opposite effect was also true: the material obtained from patients with lymphatic leukemia was claimed to retard the progress of myelocytic leukemia. These materials are known as myelokentric and lymphokentric acids, respectively.[12,13]

On the basis of the work just noted, we might postulate that there is a mutual antagonism between polynuclear neutrophiles and lymphocytes, and that although a case of infectious mononucleosis may have an absolute polynuclear count as high as or even higher than normal, this force is relatively ineffective in the presence of a tremendous increase in the number of lymphocytes.

Penicillin in daily doses of 600,000 units of procaine penicillin-in-oil tides these patients over this relatively granulocytopenic period. We believe, with Joyce, that penicillin is an important part of the treatment of the complicating sore throat in infectious mononucleosis, in spite of statements by recent authors on the subject of penicillin stating that it should not be used in infectious mononucleosis.[9]

Joyce has also called attention to the "saddleback" type of fever, i.e., a recurrent type of fever, associated with the severe ulcerative pharyngitis. This phenomenon was noted in three of our patients.

TREATMENT OF ASSOCIATED HEPATITIS WITH LIPOTROPIC SUBSTANCES

It would be safe to say that clinical or laboratory evidence of hepatic involvement occurs in at least 60 to 75 per cent of the cases of infectious mononucleosis. Some authors report 95 to 100 per cent[3,4,8] involvement as shown by abnormalities in the liver function tests in cases of infectious mononucleosis without jaundice. In fact, a highly positive cephalin flocculation test with classical symptoms may speak in favor of this disease in spite of a negative heterophile antibody reaction.

We have found that the earliest symptom heralding liver involvement is severe unremitting nausea, sometimes associated with fullness and belching. In the presence of these symptoms, the cephalin flocculation test would invariably be highly positive (3+ to 4+). Giving these patients choline dihydrogen citrate (tablet gr 10, Lilly, or capsule gr 7.5, Flint) or methionine (gr 7.5 tablet or capsule) every four hours produced a dramatic remission of the nausea and other associated hepatic symptoms within twenty-four to thirty-six hours. We have never observed jaundice in any of our personal cases when the lipotropic substances were started at the onset of nausea. One of our borrowed cases developed jaundice, preceded by nausea three days before. Choline was started when fairly

deep jaundice was noted, and it seemed to improve the symptoms, according to the attending physician.

It has been repeatedly reported that the lipotropic substances do not influence the course of infectious hepatitis. It is our feeling that choline and methionine do quite dramatically affect the hepatitis of infectious mononucleosis. It might be that the hepatitis associated with this condition is of a milder type than true infectious hepatitis.

THE TREATMENT OF INFECTIOUS MONONUCLEOSIS WITH AUREOMYCIN

To date, we have used Aureomycin in eighteen cases of infectious mononucleosis as soon as this diagnosis was made. It seemed to have a remarkable influence in diminishing the fever and the size of the liver and spleen. In two cases, in which it was given early before any liver involvement was noted clinically or by test, hepatitis did not develop. This may have been fortuitous. When Aureomycin was started late in the granulocytopenic-sore throat period, it did not appear to be effective. One limiting factor in the use of Aureomycin is the nausea and vomiting that it induces in a fair number of patients. In two patients we had to return to the treatment with antihistaminic agents to obviate these by-effects.

Aureomycin apparently attacks the virus etiological agent in this condition, while the antihistamine attempts to alter the allergic substrate which we feel is present.

In two of our cases of undoubted infectious mononucleosis with relatively low heterophile antibody titers (agglutinations up to and including 1/64), the titers promptly fell after Aureomycin was started. It is possible that Aureomycin stops the development of the disease, but this point requires much further observation.

Aureomycin is given in 0.25 gram capsules every four hours, but the dosage may be increased in severe infections.

ILLUSTRATIVE CASES

Case 1.—L.M., twenty-three, a married woman, gave a history that during March, 1947, she was jaundiced for two weeks, then developed what was considered to be a virus pneumonia which lasted four weeks. Following this she developed chills with fever and sore throat for which penicillin was given by hypodermic and by mouth. However, for the following two months she still had sore throat and fever. She was seen by one of us on July 1, 1947. She also gave a history of recurrent bronchial asthma since the age of two, which developed every time she had a cold. Examination revealed a red throat, generalized adenopathy and an enlarged spleen. The white blood count was 13,000, polymorphonuclear cells 45 per cent, lymphocytes 46 per cent and eosinophiles 5 per cent. The heterophile antibody test was positive up to and including a dilution of 1/224. Agglutination tests for typhoid, brucellosis and paratyphoid A and B were negative.

Pryibenzamine, 50 mg and aspirin 5 grains were given every four hours; and within seventy-two hours there was a clearing of the redness of the throat, a marked diminution in the size of the glands, and a diminution in the size of the spleen. Within a week the patient was sufficiently recovered to take a trip to a distant city.

Case 2.—A.N., a girl, aged fifteen, complained of fever, severe sore throat, and generalized adenopathy of one week's duration. There was no liver or spleen felt in the abdomen. Because blood work could not be done for several days, a large dose of penicillin was given, which had no effect on any of the symptoms. A heterophile antibody test was positive up to and including a dilution of 1/224. The white count was 14,400, with 44 per cent nertrophiles, 14 per cent large lymphocytes, 33 per cent small lymphocytes, and 8 per cent monocytes. Many large lymphocytes appeared to be in transition to monocytes.

The patient has a marked allergic family history. She, herself, is sensitive to grass and ragweed pollens and dust. Since penicillin and aspirin had previously failed to affect her temperature, she was given Pryibenzamine 25 mg every four hours. In addition, an aspirin tablet was given at the same time. This combination had a remarkable influence on the fever and sore throat. The generalized lymphadenopathy remained for five days longer, and the patient was clinically well in about ten days.

Case 3.—C.E., aged twenty-four, with a previous history of thrombocytopenic purpura ten years previously, became ill with a fever of 103 to 104 degrees and severe unremitting nausea. She was treated expectantly with acetysalicylic acid and other simple remedies for several days. She was seen by one of us three days after the onset of this illness, and after careful examination we found only a high fever and complaints of severe nausea. Methionine, 1 gm every four hours was given because it was felt that perhaps this nausea was a product of liver dysfunction. After several days of this therapy, the nausea was much improved, but the fever still ranged between 103 and 104 degrees. The mother reported that one day this patient started to sneeze incessantly and that she developed recurrent hives with severe itching over a six-hour period. Another interesting point in her history was that she has a perennial vasomotor rhinitis, which is undoubtedly also of an allergic nature. She was seen again, and this time enlarged lymph glands were found in the neck and axilla. The spleen was enlarged. (The previous condition of thrombocytopenic purpura was treated medically and not by a splenectomy).

The patient was put on Pyribenzamine, and after twenty-four hours the temperature dropped to 100.6 degrees and she felt much better. The glands and spleen had slightly receded. At that visit the liver was also found to be enlarged, so that methionine was continued.

The blood report taken on the first visit showed a positive heterophile agglutination, being positive in dilutions up to and including 1:3584. The white blood count was 12,200, with 12 per cent adult polymorphonuclear, 3 per cent stab cells, 24 per cent large lymphocytes, 54 per cent small lymphocytes, 4 per cent monocytes and 3 per cent eosinophiles. Many of the large lymphocytes showed dark blue vacuolated cytoplasm. Two days later she developed a very severe sore throat without a membrane. A blood count taken on that day showed a total white blood count of 10,500, with 6 per cent adult polymorphonuclear, and 2 per cent stabs. The large lymphocytes showed the characteristics described above. The heterophile agglutination test was still positive in the same dilutions. Penicillin-in-oil was started, 600,000 units daily.

Five days later the white blood count was 8,200, with an adult polymorphonuclear count of 11 per cent and 3 per cent stabs. There were 10 per cent large lymphocytes and 71 per cent small lymphocytes. The large lymphocytes still showed the dark blue vacuolated cytoplasm. Penicillin-in-oil was continued.

From this point on her recovery was uninterrupted. The spleen and liver were normal size and the glands had either entirely receded or had become very small.

Case 4.—H.R., aged twenty-one, was seen on January 25, 1949, with a history of fever up to 103 degrees, severe headache, and pain in the back of the neck. Up to this time he had been on penicillin and aspirin without satisfactory relief and without improvement. He had a slightly infected throat, as well as generalized adenopathy. He had at that time no enlargement of the liver or spleen, and no rash. Agglutinations for typhoid O, typhoid H, paratyphoid A, paratyphoid B, Proteus OX19, and Brucella abortus were negative. The urine examination was normal. There were no malarial parasites seen on the smear. The heterophile agglutination was considered negative, since there was agglutination present up to and including a dilution of 1:56. The hemoglobin and red blood count were normal. The white blood count was 5,600, with 40 per cent neutrophiles (27 per cent adult polymorphonuclear, 9 per cent stabs and 4 per cent juveniles), 19 per cent large lymphocytes and 36 per cent small lymphocytes and 5 per cent monocytes. Occasional large lymphocytes showed much dark blue cytoplasm with vacuoles. These are the Downey cells seen often in infectious mononeucleosis, as well as other virus infections. Cephalin flocculation test done that day, reported two days later, showed a 3+ flocculation in forty-eight hours.

This patient's mother is a highly allergic individual and the patient himself, although not complaining of allergy in youth, stated that he had recently become markedly intolerant of orange juice, developing hives after partaking of even small quantities.

On the basis enunciated previously the patient was given Pyribenzamine, 25 mg every four hours, and an aspirin tablet with each dose. The fever fell to normal in twelve hours and remained at this level throughout the entire course of the illness. He could not take Pyribenzamine for very long because of severe side reactions, so it was changed to Trimeton ½ tablet every four hours. In addition, on this day he complained of fullness, nausea and vomiting; and he was given choline dihydrogen citrate, two 10-grain tablets, three times a day. This caused a prompt remission of his symptoms within twenty-four hours.

The following day the white blood count was 9,200, 34 per cent total neutrophiles, (26 per cent were adult types and 8 per cent were stabs). An occasional large lymphocyte showed the cytoplasm described above. On this day he developed severe pain in his throat, with a heavy grayish-black membrane appearing over a considerable area in the right pharyngeal wall. The throat smear showed occasional Gram-negative coffee-bean-shaped diplococci, occasional Gram-negative rods, and rare Borrelia vincenti; but no organisms were seen that morphologically resembled Corynebacter diphtheriae. A heterophile antibody test was still negative. Two days later the total white blood count was 11,100, with 29 per cent neutrophiles, of which 25 per cent were adult forms and 4 per cent were stabs. The heterophile antibody test was still negative.

On January 31, the heterophile antibody test became positive, with agglutinations present in dilutions up to and including 1:224. The white blood count on this date was 10,400, with 10 per cent adult polymorphonuclears and 6 per cent stabs, 26 per cent large lymphocytes and 40 per cent small lymphocytes; and the large preponderance of young lymphocytes showed the dark blue cytoplasm characteristic of Downey cells.

Large amounts of penicillin (600,000 units procaine penicillin-in-oil) were given three times daily. There was no marked improvement in the throat pain during the next several days. On February 3, the white blood count was 9,400, with 32 per cent adult polymorphonuclears and 3 per cent stabs. A direct smear of the throat showed the same organisms described above, and a throat culture showed many Gram-negative coffee-bean-shaped diplococci and occasional Gram-negative rods. The

heterophile agglutination test was now negative again. At this time Aureomycin ½ gm every four hours (1½ gm daily) was given in addition to the penicillin. There was still no apparent improvement either in the pain in the throat or in the membrane. On February 7, the white blood count was 8,600, with 34 per cent adult polymorphonuclears and 6 per cent stabs and 1 per cent juveniles, and the cytology was normal.

These measures were continued until February 10, when the throat was improved. The white blood count at this time was 6,300 and had 37 per cent adult polymorphonuclears and 1 per cent stabs, 3 per cent large lymphocytes and 52 per cent small lymphocytes, with normal cytology. The patient improved markedly. At this time, both penicillin and Aureomycin were discontinued. He was placed on pyridoxine 10 mg three times a day, and folic acid 5 mg three times a day, as well as multivitamin capsules.

Case 5.—S. R., a woman aged 21, first developed a well-authenticated case of infectious mononucleosis while at school during November of 1948. At that time she had generalized adenopathy, headaches and fever. She had what was diagnosed as Vincent's tonsillitis two weeks before this episode. On examination two weeks later, when she had come back home, her glands had receded, but her spleen was still slightly enlarged. Pyribenzamine ½ tablet three times daily was given, as well as vitamin B complex capsules. She improved markedly and was able to return to school within ten days. The patient has hay fever of the ragweed type and is exquisitely sensitive to poison ivy.

The patient was again seen on February 21, 1949, with generalized adenopathy, high fever (104 degrees), and sore throat. She was hospitalized at school, but since she did not improve, she was brought home. When seen on this visit her white count was 4,300, with 33 per cent adult polymorphonuclears, 2 per cent stabs, 15 per cent large lymphocytes, 40 per cent small lymphocytes, 3 per cent monocytes, 5 per cent eosinophiles and 2 per cent basophiles, with a moderate number of young lymphocytes showing much dark blue slightly vacuolated cytoplasm. The heterophile agglutination test at this visit was negative. However, she presented undoubted evidence of infectious mononucleosis. She was put on Aureomycin 250 mg every four hours. Within sixteen hours her throat had cleared, the glands had diminished in size and she felt very much improved. Within thirty-six hours the glands had all but become normal in size.

That day, however, the patient developed severe nausea, fullness, vomiting. Suspecting liver dysfunction, although the liver was not enlarged, she was given one tablet (10 grains) of choline dihydrogen citrate four times daily. At that time also a cephalin flocculation test was done which showed a four plus flocculation in twenty-four hours. On choline therapy the nausea, fullness and vomiting ceased and has not returned.

Case 6.—Dr. R. W., aged twenty-two, developed a sore throat, fever and glands in the neck. The fever and sore throat cleared after three days. One week later the patient again developed a severe sore throat, fever of 104 degrees, cough and generalized adenopathy. The liver and spleen were not felt. A blood count revealed 9,300 WBC with 43 per cent polymorphonuclear cells, with 20 per cent large lymphocytes and 33 per cent small lymphocytes. Occasionally large lymphocytes showed the dark vacuolated cytoplasm as seen in infectious mononucleosis. The heterophile agglutination test was positive in all dilutions up to and including 1/224. The cephalin flocculation test was negative. Aureomycin 0.25 gm was given every four hours with a reduction in fever to normal within twenty-four hours, and a remarkable reduction in the size of the glands within seventy-two hours. At this time he

complained of right lower quadrant pain, but as this was accompanied by only slight tenderness and no spasm, a diagnosis of possible abdominal lymphadenopathy was made. In any event, continuation of Aureomycin for two additional days cleared this condition completely. There were no findings in the chest. One day later, he developed itching of the soles of the feet, which was relieved in twenty-four hours with Trimeton, one tablet three times a day. From this point on recovery was uninterrupted and rapid.

Although this patient did not acknowledge any manifestations of allergy himself, it is to be noted that his brother has ragweed hay fever.

Case 7.—J. G., twenty-one-year-old man, college student, complained of a severe sore throat and moderate amount of fever while at college in another state. Two days previously he was stung by a bee, but this did not disturb him. The ensuing two days he developed severe unilateral headaches, associated with nausea and vomiting. At no time previously did he have these headaches. The sore throat cleared promptly with ordinary measures. One week later he developed a sore throat again, but this time with high fever and he was sent home. Examination revealed a reddened throat, generalized adenopathy, a markedly enlarged and tender liver and spleen and a fever of 102 degrees. The patient also complained of nausea. Infectious mononucleosis was immediately suspected, and this was substantiated by the finding of typical Downey cells in the smear, a positive heterophile agglutination test up to and including a dilution of 1/448 and a 4+ cephalin flocculation test after twenty-four hours. Aureomycin was started at once in the dosage of 0.25 gm every four hours; in addition choline dihydrogen citrate 0.5 gm was given every four hours as well. The fever and nausea responded dramatically to treatment. Within forty-eight hours the glands were much diminished. At this time, however, the patient developed a remarkably severe throat, which necessitated daily injections of 600,000 units of penicillin for ten days. Within four days of starting the choline therapy, the liver was normal size, and never again throughout the period of illness was there a complaint of nausea or fullness. The blood counts are noted in the accompanying table.

Although the patient first discounted any history of allergy, a careful inquiry revealed the following: A sister was highly allergic to many foods, the patient himself could not eat chocolate, fish, or spinach without developing hives. During his first year of life he was a feeding problem because of his many food allergies and eczema. Another interesting sidelight in this patient's history was that his sister had recovered from a very severe case of infectious mononucleosis just three weeks previously. Her symptoms were quite different in that she had severe abdominal pain and high fever, and typhoid was suspected for a period of ten days. Following a stormy course, she recovered completely. She has a long history of allergy.

COMMENT

We considered a patient to have infectious mononucleosis if, in addition to the classical signs and symptoms, i.e., fever, generalized adenopathy, sore throat, enlarged liver and/or spleen, there was also a positive heterophile agglutination test, and the presence of Downey cells in the blood smear.

There were four cases with typical signs and symptoms, the presence of Downey cells in the smear, negative heterophile antibody tests, but positive

cephalin flocculation tests. These were considered to be cases of infectious mononucleosis.

For this study, a heterophile antibody test was considered to be positive if there was agglutination in dilution of 1/128 or higher. We know that some authors consider a positive test to be 1/32 or higher, but we found too many non-specific reactions in the latter dilutions.

The term Downey cell, as used in this report, corresponds to the types of atypical lymphocytes described by Downey.[7,15] The usual cell has a very large nucleus with pronounced chromatin strands. The nucleus has many pale spots, the so-called Osgood's "nuclear fenestrations." The cytoplasm varies in amount; it may be a fine basophilic rim, or if more cytoplasm is present it may have a foamy appearance. Less often other cells are seen with irregular or lobulated nuclei.

We have had no experience with a chronic phase of infectious mononucleosis as described by Isaacs.[10] The symptoms consisted of fatigue, exhaustion, aching of the legs, weakness, depression, afternoon elevation of temperature (99.8 to 101 degrees), moderate splenomegaly, low blood pressure, low blood sugar and the presence of Downey cells in the blood smear. The heterophile agglutination titers in this series were 1/64 or lower, and the symptoms persisted for three months to four years. All of the cases in our report cleared promptly after institution of our methods of treatment. However, Isaacs' patients may have had a true chronic form of infectious mononucleosis which so far has eluded us.

An interesting observation that supports part of our thesis was made by Barnard[1] in discussing Isaac's article. He stated, "Benign systemic lymphosis (infectious mononucleosis), whether acute or chronic, appears to be a reactive state seen in individuals of allergic or atopic constitutions whose lymphoid tissue is the sensitized or shock organ. Such a lymphatic reaction is seen in some persons following the imposition of any stimulus classified among the cholinergic incitants, that is infective, traumatic, radiative, allergic, or even psychogenic affection."

Barnard has extended our observations to other stimuli besides virus infections. The possibilities of this approach appear extremely interesting.

SUMMARY

We have presented some aspects of the biology of infectious mononucleosis:

1. An allergic background was noted in all our patients.
2. Many of the patients had a paucity of granulocytes in the peripheral blood at one phase of the disease.
3. The hepatitis that occurs as part of infectious mononucleosis responds well to lipotropic substances.
4. Aureomycin in usual doses effectively aborted the disease in eighteen of our patients.

REFERENCES

1. Barnard, R. D.: Letter: Medical forum on chronic infectious mononucleosis. Modern Med., 17:79, 1949.
2. Bernstein, A.: Infectious mononucleosis. Medicine, 10:85, 1940.
3. Carter, A. B., and Maclagan, N. F.: Some observations on liver function tests in diseases not primarily hepatic. Brit. M. J., 2:80, 1946.
4. Cohn, C., and Lidman, B. I.: Hepatitis without jaundice in infectious mononucleosis. J. Clin. Invest., 25:145, 1946.
5. Crosfill, J. W. L.: Pseudo-leukemic eosinophilia complicated by gangrenous appendicitis, as a possible manifestation of infectious mononucleosis, with observations on the mutual antagonism between lymphocytes and granulocytes. J. Roy. Nav. M. Serv., 31:215, 1945.
6. Custer, R. P., and Smith, E. B.: The pathology of infectious mononucleosis. Blood, 3:830, 1948.
7. Downey, H., and McKinley, C. A.: Acute lymphadenosis compared with acute lymphatic leukemia. Arch. Int. Med., 32:82, 1923.
8. Evans, A. S.: Liver involvement in infectious mononucleosis. J. Clin. Investigation, 27:106, 1948.
9. Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Penicillin: Its usefulness, limitations, diffusion and detection, with analysis of one hundred and fifty cases in which it was employed. J.A.M.A., 125:1003, 1944.
10. Isaacs, R.: Chronic infectious mononucleosis. Blood, 3:858, 1948.
11. Joyce, F. T.: Infectious mononucleosis: a consideration of the complications and a preliminary report on the use of penicillin in this disease. Arch. Int. Med., 78:49, 1946.
12. Miller, F. R., and Turner, D. L.: The leukemias. Med. Clin. N. A., 1376, (Nov.) 1944.
13. Miller, F. R.; Herbut, P. A.; Jones, H. W.: Blood, 2:15, 1947.
14. Pelner, L.: Letter, International Correspondence Society of Allergists, 10:137, 1946-1947.
15. Randolph, T. G.: Letter, International Correspondence Society of Allergists, 10:148, 1946-1947.
16. Randolph, T. G., and Barber, E. B.: Blood studies in allergy. II. The presence in allergic disease of atypical lymphocytes and symptoms suggesting the recovery phase of infectious mononucleosis. Am. J. M. Sc., 207:638, 1944.
17. Randolph, T. G., and Hettig, R. A.: The coincidence of allergic disease, unexplained fatigue and lymphadenopathy; possible diagnostic confusion with infectious mononucleosis. Proc. Central Soc. Clin. Research, 17:44, 1944.
18. Ravenna, P., and Snyder, J.: The occurrence of edema of the pharynx and larynx in infectious mononucleosis. Ann. Int. Med., 28:861, 1948.
19. Service, W. C.: Letter, International Correspondence Society of Allergists, 11:3, 1947-1948.
20. Wiseman, B. K.: Letter, International Correspondence Society of Allergists, 10:138, 1946-1947.

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PANEL DISCUSSION ON ARTHRITIS AND RHEUMATISM

One of the outstanding features of the Seventh Annual Session of the College will be the panel discussion on arthritis and rheumatism, which will occupy the entire afternoon of February 14, commencing at 2:00 p.m., with Dr. George Rockwell as chairman. Speakers will be Drs. Wm. Kaufman, M. G. Bohrod, Michael Zeller, T. F. Dougherty, and C. R. K. Johnston. A round table discussion will conclude the panel. The complete program will be announced in the November-December issue of the ANNALS.

THERAPY OF RAGWEED HAY FEVER WITH ELECTROPHORETICALLY ISOLATED FRACTIONS (ARTEFOLIN AND TRIFIDIN)

Preliminary Report

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IT has previously been shown by electrophoretic fractionation that there are numerous components in ragweed pollen extracts which are closely related antigenically.[1] In addition it was pointed out that these components vary widely in their electric charges and that the differences in electric mobility between the components could be used to purify certain of the fractions. By means of the Tiselius technique small quantities of the major colorless component, Trifidin, in giant ragweed pollen extract and the major colorless component, Artefolin, in dwarf ragweed extract had been obtained.

The present communication is a preliminary report of the results of therapy with ragweed antigens rendered essentially colorless electrophoretically. The essentially colorless fractions (approximately 90 per cent of the pigment was removed) isolated by a new method to be discussed in this communication was clinically studied in the summer of 1949 with the kind co-operation of Dr. A. Colmes, Boston, Mass.; Dr. J. Glaser, Rochester, N. Y.; Drs. H. A. Levy and L. Unger, Chicago, Ill.; Dr. L. J. Lieder, Cleveland, Ohio; Dr. A. L. Maietta, Boston, Mass.; Dr. J. H. Mitchell, Columbus, Ohio; and Dr. O. R. Withers, Kansas City, Mo. In this way an independent evaluation of the results of therapy with the mixed colorless pollen extract fractions was obtained.

It was found that with small doses of the colorless fractions in the limited series of fifty-six cases to be presented the results of therapy were about as good as the results obtained with higher doses of the crude mixtures extracted directly from the ragweed pollens as ordinarily administered.

METHOD OF FRACTIONATION

The Tiselius technique was found to be unsuitable for the electrophoretic isolation of large quantities of the colorless material. For this reason a simplified electrophoretic preparative technique was developed which was adaptable to experimental procedures at room temperature.[2]

Many attempts have been made to adapt the separation of electrically charged ions like proteins to simple equipment operable at room temperature. Membranes, sand barriers, gels, and jellies have been used to immobilize the material and thus prevent convection from mixing the protein

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(or antigen) in a solution, P, with the adjacent buffer solution, B. Tiselius[3] points out that aside from optical observations his method increases the potential gradient in the U-tube without undesirable heat convection, simplifies sampling, and avoids disturbing electrolytic processes.

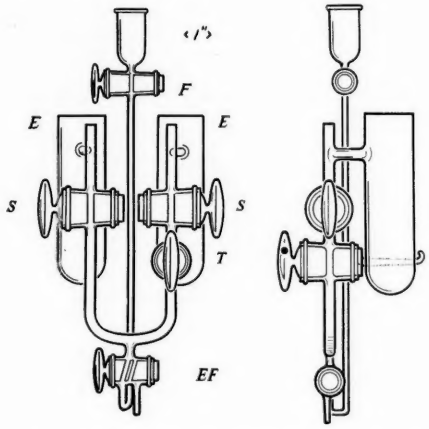

Fig. 1. Front and side views of one design of preparative electrophoresis cell employed. This diagram embodies several different designs found useful. The filling stopcock, F, is used to form the boundary through the two-way stopcock, EF. When EF is rotated and stopcock, S, is open, either the right or left side may be drained and purified material obtained. An alternate method of obtaining samples is to use the tail-hole stopcock, T. Thus, with ragweed extract, the volume of purified Trifidin or Artefolin obtained in twenty-four hours is about 1 cc. Since these solutions may be lyophilized prior to electrophoresis a comparatively large quantity of antigen may be isolated with this simple procedure.

The equipment for the preparative method described here costs, aside from the source of current, less than $50. It suitably embodies the advantages of the Tiselius method just mentioned, especially for use at room temperature without any temperature control.

The technique employs a modification of the classical U-tube (Fig. 1) with large side vessels to hold carbons or reversible electrodes. The tail-hole stopcock, T, is used for withdrawing samples at the side. Alternatively a two-way stopcock, EF, at the bottom of the U-tube, is employed both for forming the boundary and for draining the electrophoretically purified fractions from either side of the U-tube. The method depends upon controlling solutions B and P so that they will have different densities, viscosities, pH's, and conductances as follows: Solution B (supernatant) will have a high coefficient of viscosity at the pH of the isoelectric point of the protein contained in solution P, to be immobilized in the lower part of the U-tube. Solution B will have a density considerably less than solution P, so that as the boundary P-B is formed, a well-defined boundary,

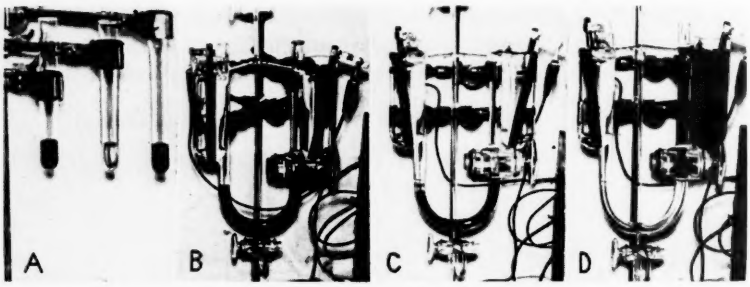

Fig. 2. Four photographs depicting the electrophoretic separation of a charged blue dye from a hemoglobin solution. This is equivalent to separation of the pigments from the major colorless component in pollen extract solutions.

(A) The types of solutions used. In the left test tube is Evans Blue; in the center test tube is the hemoglobin solution; in the right test tube is a mixture of Evans Blue and hemoglobin solutions.

(B) The start of the experiment. The boundary is formed by the hemoglobin-Evans Blue mixture. The lower part of the U-tube contains this mixture (black) in 50 per cent glycerol. The supernatant liquid (light) is 40 per cent glycerol, buffered at the isoelectric point of the hemoglobin. Note the sharp boundaries formed at room temperature.

(C) The experiment after five hours. Note that the boundary has persisted with migration of the Evans Blue (sharp boundary) toward the anode. Some of the Evans Blue can be seen in the stopcock, but both electrode vessels are clear.

(D) The experiment twenty-four hours after starting shows the migration of the Evans Blue into the positive electrode vessel. The colored photographs upon which this black and white photograph is based show that the hemoglobin remained fixed in the lower part of the U-tube with the dye migrating, as illustrated, out of the hemoglobin. These experiments represent how the colorless components of ragweed remain behind with the negativly charged pigments migrating out of the original pigmented ragweed extract solutions, leaving behind the essentially colorless fraction.

stable enough for preparative electrophoresis, results. Typical solutions used by the writer and his co-workers for the past year for the separation of Trifidin and Artefolin, the unpigmented fractions of giant and dwarf ragweed extracts, have been B-40 per cent glycerol at pH 6.8 and P-50 per cent glycerol extract of ragweed pollen. The electrical conductance of solutions B and P in the separation should be regulated so that as little electrolyte as convenient is in P, with a suitable amount in B, to control the pH and drop in potential at the beginning of the separation. For example, in the case of ragweed extracts, no saline was added to the ragweed to be fractionated in solution P. The 40 per cent glycerol in B contained M/15 phosphate buffer at pH 6.8. Thus, initially, the main drop in potential was across the material to be separated, and fractionation was facilitated. A striking experiment (Fig. 2) demonstrating this technique may be made by having solution B at about pH 6.8 employing M/15 phosphate buffer in 40 per cent glycerol, with solution P, a mixture of hemoglobin and T-1824 (a negatively charged dye), in 50 per cent glycerol. At this pH, the isoelectric point of hemoglobin is electrophoretically fixed at the boundaries, whereas the dye, T-1824, migrates out of the mixture to the anode, leaving the hemoglobin with a fairly sharp boundary at the negative side after twenty-four hours.

It may be emphasized that our method utilizes Newtonian or truly viscous liquids. The convection ordinarily resulting from the application of 450 volts to a U-tube, 60 cm long with an internal diameter of 1.0 cm,

at room temperature, is avoided by the use of only high viscosities, not plasticities; and no membranes, jellies, or similar mechanical devices are required. The temperature in the laboratories at Cold Spring Harbor during the summer of 1948 varied consideraly over twenty-four hours

TABLE I. COMPARISON OF FORMATION OF CLASSICAL TISELIUS BOUNDARIES AND THOSE OF THE MODIFIED TECHNIQUE

Tiselius Method	Method Reported Herein
Conductance B* = conductance P†	Conductance B $>>$ conductance P
Viscosity B = viscosity P	Viscosity B $<$ viscosity P
Density B = or slightly less than P	Density B $<$ density P
pH of B = pH of P	The pH of B at or close to isoelectric point of protein to be separated in solution P
Temperature controlled at or near 4° C	Room temperature fluctuations—no temperature control

*Supernatant solution.
†Lower protein solution. Note that both P and B have Newtonian flow.

but did not disturb the boundaries for preparative purposes during four-day electrophoretic separations. The apparatus can be readily used in an ice chest. If room temperature does not destroy the material to be studied, it is preferable not only because of simplicity but also because the mobilities are greater at this temperature. Table I summarizes the differences enumerated in preparative procedures with the classical method of Tiselius and the method herein described.

Ragweed extracts were made by suspending 10 gm. of ragweed pollen in 100 cc of a 50 per cent glycerol solution. Essentially colorless solutions for therapy were diluted with saline to avoid the pain of the injection of glycerol. This resulted in solutions containing not more than 1000 phosphotungstic acid precipitable nitrogen units per cc for all practical purposes. For this reason the solutions were later lyophilized before electrophoresis, and more concentrated solutions were obtained by this method. Lyophilization may be simplified if the ragweed extract is first dialyzed through No. 36/32 Visking membranes for three hours. However, high losses of active material occur. The dialysis may be followed by studying the electric conductance of the solution being dialyzed, as a function of time. It is suggested that a technique of this sort be used as an end point of dialysis. It would be desirable to avoid dialysis by using better freeze-drying equipment than that available to us.

In order to conserve the ragweed pollen and to shorten the time of the electrophoresis, a modified method was employed from which small quantities of relatively colorless fractions were obtained in twenty-four hours. Three solutions B′, P′, and B″ of different concentrations of glycerol were employed. Solution B′ was M/15 phosphate buffer in 40 per cent glycerol. Solution P′ was the lyophilized ragweed extract reconstituted

TABLE II. SUMMARY OF RESULTS OF THERAPY WITH ELECTROPHORETICALLY PURIFIED COLORLESS RAGWEED ANTIGENS BY VARIOUS AUTHORS IN THE SUMMER OF 1949.

Since it is difficult to evaluate the fine aspects of the results of therapy, two classes only were tabulated. Where the results of therapy were as good as that with the usual mixed antigen or where there is an improvement over a previous season the result is called good; otherwise the result of therapy is designated as poor. Thus a fair result would be considered poor and not good. In the cases of H.A.A. it is felt that the good results were definitely connected with the free use of various types of adjuvant therapy. Adjuvant therapy includes autogenous dust injections, antihistaminic drugs including ephedrine and epinephrine as well as sedation in certain circumstances. All patients treated are included.

Patient	Age	Sex	Clinical Diagnosis	Ragweed Therapy (Previous Year)	No. of Injections of EPR	Total Phosphotungstic Acid Units	Results of Therapy	Adjuvant Therapy	Remarks
Pa ients of H.A.A. Huntington, L. I.:									
1 DO	6	F	HF & A	Yes	23	600	Good	Yes	
2 WO	34	M	HF & A	Yes	22	685	Good	Yes	
3 JR	10	M	HF & A	Yes	10	90	Good	No	
4 BN	42	F	HF & A	No	37	3700	Poor	Yes	
5 HM	32	F	HF & A	No	14	220	Good	Yes	
6 HM	25	M	HF	No	16	2100	Good	Yes	
7 SZ	13	M	HF	Yes	16	280	Good	Yes	
8 RW	5	M	HF & A	Yes	15	2700	Good	Yes	
9 HS	29	M	HF & A	Yes	20	800	Good	Yes	
10 ML	34	F	HF & A	Yes	15	1850	Good	No	
11 MJ	22	M	HF & A	No	11	165	Good	Yes	Coseasonal Intra.
12 GH	9	M	HF & A	No	11	95	Good	Yes	
13 MF	9	F	HF & A	Yes	9	900	Poor	Yes	
14 AD	7	M	HF & A	No	27	840	Good	Yes	
15 EB	23	F	HF & A	Yes	23	1815	Good	Yes	
16 FC	7	F	HF & A	No	18	420	Good	No	
Patients of H.A.A. New York City									
17 DC	28	F	HF & A	Yes	20	2200	Good	No	
18 DL	30	M	HF & A	Yes	20	4300	Good	Yes	
19 EC	26	F	HF	No	5	10	Poor	Yes	
20 KW	24	F	HF & A	Yes	5	230	Poor	Yes	
21 KS	15	M	HF	Yes	14	400	Good	No	
22 JK	27	M	HF & A	Yes			Poor	Yes	
23 BF	27	M	HF & A	Yes	23	5700	Good	Yes	
24 LL	30	M	HF	No	12	1400	Good	Yes	
25 PL	50	M	HF & A	Yes	19	6600	Poor	No	Good for Asthma
26 PC	22	M	HF & A	No	27	13400	Good	Yes	
27 JD	17	M	HF	Yes	18	2690	Good	Yes	
Patients of L. L. Maietta, Boston									
28 RV	33	M	HF	No	11	290	Good	No	Intradermal
29 MM	14	F	HF	No	12	214	Good	No	Intradermal
30 KT	8	M	HF	No	13	285	Good	No	Intradermal
31 LP	38	F	HF	No	11	310	Poor	No	Intradermal
Patient of J. H. Mitchell, Columbus, Ohio									
RT	64	F	HF & A	Yes	12	To Aug. 6 Approx 2000	Poor		
Patients of J. Glaser, Rochester, N. Y.									
32 R	17	M	HF & A	Yes	15		Poor		No Asthma
33 L	16	F	HF & A	Yes	9		Good		
34 S	6	F	HF	No	37		Poor		

TABLE II.—CONTINUED

Patient	Age	Sex	Clinical Diagnosis	Ragweed Therapy (Previous Year)	No. of Injections of EPR	Total Phosphotungstic Acid Units	Results of Therapy	Adjuvant Therapy	Remarks
Patients of Herman A. Levy and Leon Unger, Chicago, Ill.									
35 LL	22	F	HF	No	25	1700	Good	Yes	
36 EG	31	F	HF	No	28	4800	Poor	Yes	
37 DG	5	M	HF	No	35	1580	Good		
Patients of L. J. Lieder, Cleveland, Ohio									
38 CD	44	F	HF	Yes			Good		
39 SG	61	F	HF	No			Poor		
40 JB	14	F	HF	Yes			Poor		Max. dose 5 U followed by severe local reac.
Patients of A. Colmes, Boston, Mass.									
41 KO	40	F	HF	Yes	9	2050	Good		
42 HC	40	M	HF	No	23	2300	Good		Better than '48.
43 AM	26	F	HF	Yes	14	3600	Poor		Constitutional
44 BL	35	F	HF	Yes	10	2801	Good	Yes	Highly sensit.
45 MF	35	F	HF		12	150	Good		Very sensit.
46 EA	30	F	HF	Yes	8	3100	Good		Same as old method
47 NM	36	F	HF	Yes	20	4600	?		Not conclusive
48 BR	32	M	HF	Yes	22	11000	Good	Yes	Same as old method
49 JF	20	M	HF	Yes	13	3500	Poor	Yes	Same as old method
50 MH	45	F	HF	Yes	14	4100	Poor		Mild constitut.
51 JK	27	M	HF & A	Yes	5	2100	Good	Yes	Same as old method
52 MG	35	M	HF	Yes		290	Good		Constitutional
Patients of O. Withers, Kansas City, Mo.									
53 RP	28	M	HF	Nc	24	360	Good	Yes	
54 CK	24	M	HF & A	No	20	690	Good	Yes	Asthma preceding season
55 RP	23	M	HF & A	Yes	19	110	Good	Yes	Poor W. Kan. other pollen.
56 BF	21	M	HF	No	11	60	Poor	Yes	Coseas.

with 45 per cent glycerol to 20 cc. Four cc of solution P′ was run through F-EF. Solution B″ was M/15 phosphate buffer in 50 per cent glycerol as the second buffer separated from the supernatant by P′.

Another modification of the U-tube consisted of a second tail-hole stopcock so that both positively and negatively charged products can be drained off.

The U-tube is filled with the solution of the concentration of glycerol, B′, through EF so that the liquid level rises above the stopcock S. About half an hour is permitted to elapse for test of leakage. After this period, the electrodes are placed in the vessels, E, and the solution B′ is run in until the U-tube and the electrode vessels are filled so that the bridge between the U-tube and vessels is also filled. Precautions are taken not to allow any air bubbles to enter the system. The next dense solution, P′, is added, approximately 4 cc or enough to fill the tube between the stopcock S and T. This volume must be calibrated for each U-tube. After the solution P′ is allowed to run into the U-tube, solution B″ is used to raise the solution P′ to the desired level.

The foregoing general method has been employed with urea and sugar, using the hemoglobin-dye mixtures, and has been found to be effective, using these materials to form solutions of high and different densities.

RESULTS OF CLINICAL TRIALS

The colorless fraction (on the basis of phosphotungstic acid precipitable nitrogen) used in this series of clinical trials seemed to be less skin reactive than the mixture. What the meaning of this is will be discussed in more detail shortly. The method of electrophoretic preparation was begun in the summer of 1949 and had not yet reached the point to which it has now advanced. For this reason the largest dose was 1,000 PTA units per cc. Table II is a summary of the results obtained by the collaborating physicians mentioned in the introduction and by the writers. Essentially colorless antigens of both giant and dwarf pollen were employed. In all likelihood about 10 per cent of the pigment remained. For this reason the immunologic results are influenced by the presence of a small amount of pigment. The method of deciding whether the clinical results were good or poor was as follows: If the results of therapy were obviously good, they were classified as good. Or if the results were as good as had been obtained previously with the whole extract, they were classified as good. If they were almost as good as previous results, they were classified as poor. In other words, the patients' condition had to be either equal to or better than previous experience or the comparative classification of poor was given. The patients were treated over a wide geographical area so that approximately equal numbers of patients were treated by the writers and their collaborators. As indicated in the table, small doses of pollen allergens were given throughout the season. The number of injections given varied between five and thirty-seven with no regularity essentially observable in the results as far as the number of injections go. A similar lack of regularity exists in the relationship of whether a good or poor result was obtained relative to the dosage.

Let us first consider the patients of the writer treated both in Huntington, L. I., and in New York City. For practical purposes it will be desirable to group these patients together. The writer treated twenty-seven patients with hay fever or with hay fever and asthma with adjuvant therapy in nearly all the cases. The results may be briefly summarized as follows: Twenty-one of twenty-seven were classified as "good." As mentioned, in practically all of these cases adjuvant therapy was employed. This included autogenous dust injections, antihistaminic drugs, ephedrine, and epinephrine with sedation in certain circumstances. Psychotherapy, which takes place in all relationships between doctor and patient, must also be included but this cannot be evaluated at this time. In the writer's series, then, 77 per cent of the patients are classified as good. In the remaining series, the patients of Drs. Maietta, Glaser, Levy, Unger, Lieder, Colmes, and Withers, there were thirty patients. In the thirty patients that were treated, there were twenty-nine usable for classification. Of these twenty-nine cases eighteen cases can be evaluated as having had a good result. In the series of the collaborators, then, 62 per cent are classified as good, the average for the whole series being about 70 per cent. These results are considered

satisfactory as a pilot test of the electrophoretically purified antigens, considering the small dosage employed throughout.

DISCUSSION

Although skin tests made by the writers showed that the electrophoretic fractions were usually less active than the crude mixture, reports from the collaborators indicated that this was not necessarily so. It is possible that the similarity of antigenicity reported previously by the writer for the colorless fraction and the fast-moving pigment fraction as well as other pigments, as far as these experiments went, might have to be modified by future experiments. It is also possible that there were fluctuations in the temperature in the electrophoretic apparatus which may have led to the deterioration during the separation. Different individuals may eventually be shown to have different types of sensitivity to the various fractions. Fractions now being isolated indicate that powerful antigens are being obtained by the method now reported.

It has been shown by ultracentrifugation that the colorless fraction is identical with the main molecule having the highest molecular weight found in the crude mixtures. The value of this molecular weight is about 5000. Reports claiming the presence of "large" molecules often describe[1] contaminated debris present in very small quantity found in colloids of the type studied, or[2] artefacts produced by prolonged dialysis which lead to the formation of molecular aggregates and artificial systems not found in nature. It is our opinion that in freshly prepared ragweed extracts not subjected to involved laboratory procedures, which inevitably lead to molecular aggregation, the largest molecule present of antigenic significance in the production of and therapy of ragweed pollen hay fever is not much larger than 5000 in molecular weight, exemplified by the electrophoretically homogeneous fractions, Trifidin and Artefolin. It is our working hypothesis, evidence for which is provided in this communication, that this molecule may, in higher doses than that employed here, provide better protection to the patient with ragweed pollen hay fever and asthma than high doses with crude mixtures.

SUMMARY

1. With the co-operation of a group of allergists in different parts of the United States, electrophoretically purified colorless ragweed antigens (Trifidin and Artefolin) were used in the therapy of fifty-six cases of hay fever and asthma.

2. A new preparative method for obtaining these antigens with simplified electrophoretic equipment is described. The method comprises the control of heat convection by using liquids of high coefficients of viscosity and low conductance, making the technique practical at room temperature.

3. Because of losses encountered in purification only small doses of pollen antigen were available for therapy. It was found, on the basis of

this small series, that good results were obtained in 70 per cent of the patients treated. It is believed that (a) in freshly prepared ragweed extracts (not subjected to elaborate laboratory procedures which lead to molecular aggregation) the largest molecule of antigenic significance in the production of and therapy of ragweed pollen hay fever is of the order 5,000 in molecular weight, and (b) it is this molecule that is responsible for the favorable results reported here in the therapy of ragweed hay fever and asthma.

4. This molecule (M.W. = 5,000 approx.) may, in higher doses than that reported here, provide better protection to the patient than the high doses of crude mixtures of ragweed pollen extracts.

BIBLIOGAPHY

1. Abramson, H. A., Sookne, A. M., and Moyer, L. S.: Electrokinetic phenomena. XIV. The inactivation of ragweed pollen extracts by adsorption and electric charge of the resultant surface. J. Allergy, 10:317, 1939.
Abramson, H. A., and Moore, D. H.: A discussion of electrophoresis with special reference to serum and allergens. J. Lab. & Clin. Med., 26:174, 1940.
Abramson, H. A., Moore, D. H., Gettner, H. H., Gagarin, J., and Jennings, L.: Electrophoretic isolation of constituents of ragweed pollen extracts. Preliminary note. J. Am. Chem. Soc., 62, 16:27, 1940.
Abramson, H. A., Moore, D. H., Gagarin, J., Jennings, L., and Gettner, H. H.: Isolation of an unpigmented skin reactive constituent from extracts of ragweed pollen by electrophoresis. Proc. Soc. Exper. Biol. & Med., 44:311, 1940.
Abramson, H. A.: The nature of the ragweed pollen allergen. Tr. New York Acad. Sc., 4: series II:55, 1941.
Abramson, H. A.: Skin reactions. X. Preseasonal treatment of hay fever by electrophoresis of ragweed pollen extracts into the skin. J. Allergy, 12:169, 1941.
Abramson, H. A., Moore, D. H., and Gettner, H. H.: An electrophoretically homogeneous component of ragweed producing hay fever. Proc. Soc. Exper. Biol. & Med., 14:153, 1941.
Abramson, H. A., Engel, M. G., and Moore, D. H.: Skin reactions to electrophoretic fractions of timothy pollen extract. J. Allergy, 14:65, 1942.
Abramson, H. A., Moore, D. H., and Gettner, H. H.: Electrophoretic and ultracentrifugal analysis of hay-fever-producing component of ragweed pollen extract. J. Phys. Chem., 46:192, 1942.
Abramson, H. A., Moore, D. H., and Gettner, H. H.: A general electrophoretic pattern in extracts of pollens causing hay fever. J. Phys. Chem., 46:9, 1942.
Abramson, H. A.: Chemical, physical and immunological properties of electrophoretically purified pollen extracts. Ann. Allergy, 5:19, 1947.
2. Abramson, H. A.: Simplified preparative electrophoresis at room temperature. Science, 110:716, 1949.
3. Tiselius, A.: XI. International Congress of Pure and Applied Chemistry. P. 9. London: 1948.

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FIRST INTERNATIONAL CONGRESS ON ALLERGY

The American Express Company is preparing itineraries for the first meeting of the International Association of Allergists at Zurich, September 23-29, 1951. Those considering attendance should write Dr. F. W. Wittich, Executive Secretary, at 424 LaSalle Building, Minneapolis, for complete information.

ANTHOCYANINURIA AND BEET ALLERGY

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ANTHOCYANINURIA, the presence of vegetable pigment in the urine, has been observed by us following the ingestion of beets in individuals manifesting an allergic reaction. Twenty-eight cases are herein presented, twenty-six of which were associated with beet allergy, while the appearance of the pigment in the urine of two seemed to have been related to allergic reactions to other foods coincident with the ingestion of beets at that same time or shortly afterward. It is felt that the presence of an allergic reaction explains why certain individuals manifest this phenomenon after feedings of beets while in others it cannot be demonstrated. To our knowledge the association of anthocyaninuria with allergy has not been previously pointed out.

The first available report of anthocyaninuria was by Jervis[6] in 1914 when he described red urine in the case of a seven-year-old girl who developed sore throat, headache, pain in the abdomen with nausea, vomiting and resulting ketosis after having eaten beets.

Hess and Myers[4] in 1919 in a paper discussing carotinemia stated that certain children after the ingestion of beets showed a red pigment in the plasma and urine while in others the feeding of extraordinary amounts of beets or beet juice did not produce these findings. They attributed this to an individual variation in the absorption of the pigment.

The experiments of Horwitt[5] in laboratory animals are of interest. He made an extract of anthocyanin chloride from Concord grapes and injected it subcutaneously into rats and observed the pigment in the urine. He then fed this extract to rats and subsequently observed it in the feces but not in the urine. The intestinal flora of rats did not seem to destroy this anthocyanin. In a dog the intravenous injection of the extract resulted in its excretion in the urine and the lymph, whereas the intubation of the material with milk into the duodenum of the same dog did not result in pigmentation of the urine. Rabbits fed this anthocyanin were the only experimental animals tested which excreted the pigment in both the feces and urine.

Ruh and Garvin[17] in 1924 reported thirty cases of anthocyaninuria in children after beet ingestion. Successful attempts to reproduce the condition occured in only eight out of fifteen of the above cases. They concluded that the inconsistency in producing red urine in all patients after beet ingestion or of reproducing it in the same patient was not due to an "individual variation in the absorption of the pigment" as suggested by Hess and Myers,[4] nor to an idiosyncrasy in metabolism but was dependent upon the amount of anthocyanin in the beets themselves and to the amount of beets

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ingested. Blood serum was examined in three of the cases of anthocyaninuria four hours after beets were eaten and a dull red pigment was observed.

Poole[8] cited a case of anthocyaninuria in 1927 occurring coincidentally with nephritis in which the red color of the urine was thought to have been due to the presence of blood in the urine. The history included unexplained insomnia, restlessness and epigastric pain immediately after meals. However, urinalysis failed to reveal the presence of red cells in the urine, and spectrographic studies did not reveal bands characteristic of hematoporphyrin. The color of the urine changed to yellow when alkali was added and returned to red upon acidification. The presence of the anthocyanin in the urine of this case was attributed to changes in the permeability of the kidneys associated with the nephritis.

Individual cases of red pigment in the urine of well children after having eaten beets were noted by Matheson[7] in 1936 and Hallé and Girard[3] in 1938.

Cathala, Martrou and Gras[1] in 1939 observed a patient with beet pigment in the urine without further symptoms and then deliberately re-fed beets to the child and were able to reproduce the pigmentation of the urine. They noted that the urine was acid and on that basis placed three other children on a ketogenic diet, calcium chloride and phosphoric acid so that the urines were pH 4.6, 4.4, and 4.4, respectively. They were fed 125 grams of beets, and in one case the urine remained unpigmented while in the remaining two the urine took on a "roseate tint." On this basis they concluded that the passage of the pigment into the urine takes place in subjects having an acid urine.

Our attention was first drawn to anthocyaninuria in the case of a young man seen in 1941 whose family history was positive for allergic disease and who, at the age of twenty-eight, had a gastric resection for peptic ulcer with recurrent bleeding. For the previous ten years he had had hay fever each May and June and recently complained of hives. For several years he had excessive gas and a feeling of fullness particularly after his breakfasts and evening meals. He was aware that wheat, shell fish, chocolate, and tea tended to produce these symptoms. He also complained of chronic constipation with mucus in the stools. X-ray studies revealed a well functioning gall bladder and gastrojejunal stoma. The barium enema showed evidence of a spastic colon. The findings on gastroscopic examination were compatible with a diagnosis of a chronic superficial gastritis. Laboratory studies were normal except that the blood smear revealed an 8 per cent eosinophilia. Stool examinations for parasites and ova were negative. Intradermal skin tests to foods and inhalants revealed major sensitivities to wheat, chocolate, string beans, and the grass pollens.

The patient was hospitalized at the time and placed on a diet including wheat and string beans. On one occasion after an evening meal containing wheat and beets he experienced abdominal cramps, nausea, and vomiting. Shortly after the meal he had a bowel movement which was colored red and

noted that his urine was the color of port wine. This urine specimen was examined and found negative for blood pigment; the color changed to yellow upon alkalinization and back to red when acidified, in a fashion observed with beet juice. It was therefore concluded that this might be beet pigment from the meal eaten prior to the collection of the specimen. After the production of these symptoms, wheat, chocolate, string beans, and tea were removed from the diet for several days, and the patient experienced complete relief from his symptoms. During this period he had been deliberately fed beets twice daily in an effort to reproduce the condition, but the urine remained normal in color. He was then fed string beans along with beets at the same meal, which was promptly followed by abdominal cramps, nausea, vomiting and again he passed a port wine colored urine. Subsequently he was fed wheat and beets at the same meal on two successive days with the reproduction of the gastrointestinal symptoms and the appearance of the pigmented urine. At this time wheat, beans, chocolate, and tea along with shell fish were eliminated from the diet with relief of the digestive symptoms, and the patient left town before any further studies with the beet pigment could be made. It was felt that the patient's allergic reactions to wheat and beans had played some role in allowing the beet pigment to be absorbed from the intestinal tract in sufficient quantity to be excreted in the urine.

Searching for possible etiological factors in this case, it was noted that Cathala et al contended that anthocyaninuria was related to the acidity of the urine. We selected three controls at random who were fed large servings of beets three times a day for two weeks after the urine had been maintained at a pH of 4.5 by ammonium chloride administered by mouth. At no time during this experiment did any of the controls have beet pigment in the urine or have any untoward reaction following the ingestion of beets.

After the first observation of this phenomenon we continued to search for other cases. Peculiarly enough this opportunity presented itself in 1946 under unusual circumstances. One of the controls, who had eaten beets three times a day for two weeks without anthocyaninuria in the above mentioned experiment, five years later sought allergic management for headache, nasal stuffiness, fatigue, abdominal cramps and unexplained diarrhea. He had been placed on an elimination diet with relief of symptoms, and then foods were added in the escalator fashion until the diet list was completed. He was found allergic to several foods, so carbohydrate was urged to make up the caloric requirements, and this was taken largely in the form of beet sugar since the patient lived in Michigan where sugar is largely from this source. He had eaten beet sugar several times daily in moderately large quantities over a period of seven months. Beets as such were ingested only occasionally.

His wife also had been under allergic study during the same period for

severe and frequent headaches with nasal stuffiness which were relieved by combined inhalant and diet therapy. She, too, ate large quantities of beet sugar over the same period of time.

Seven months after the beginning of the allergic diets high in incidence of beet sugar, both the former control and his wife noted red urine after having eaten liberally of pickled beets. Urinalysis revealed the absence of red cells or albumen and also gave negative tests for blood pigment. The urine changed to yellow when alkali was added and returned to red when acidified. The pH of both specimens was 5.

The observation of anthocyaninuria in a patient subsequent to the development of a proven food and inhalant allergy and in whom six years previously we were unable to produce the condition experimentally by massive and prolonged ingestion of whole beets added weight to the original suspicion that allergy played some part in the production of this phenomenon.

After these original observations the former control and his wife deliberately underwent test feedings with beets alone on eleven different occasions and each time clinical allergic reactions were observed, followed in from three to eight hours by the appearance of port wine colored urine.

Three individual eating tests to whole beets were performed on both individuals after the manner originally described by Rinkel[15] and modified slightly by Randolph and Rawling.[10] The husband, or former control, reacted clinically on all three occasions with nasal stuffiness, vertigo, nuchal headache, regurgitation and chilliness. The wife complained of nasal stuffiness, frontal headache with nuchal pain and nuchal muscle spasm. After the experimental beet ingestion, both individuals subsequently showed anthocyaninuria; all six tests were provocative of a leukopenic response of between 40 to 50 per cent in the serial white cell counts such as described by the above authors.

Before any further investigation was carried out, it was deemed advisable to determine whether the pigment in the urine was the same as that found in beets.

The procedure of Pulcher, Curtis and Vickery[9] was used to isolate a quantity of pure pigment from canned beets. The following modifications were made in their procedure. Canned beets were used rather than fresh beet roots since they were fed in this form on the individual eating tests. The beets were first broken up in a Waring Blender and the juice extracted. The beet juice obtained from six No. 10 cans of whole beets was lyophilized. The remainder of the procedure for isolating crude betanin was the same as that given by the above authors. In this way 43 grams of crude betanin were isolated.

Five grams of crude betanin were further purified and crystallized yielding 80 mg. of crystalline material. The purified betanin was dissolved in anhydrous methyl alcohol containing 4 per cent hydrochloric acid and an absorption curve was obtained using a Beckman Quartz Spectrophotometer (Fig. 1).

About one liter each of pigmented and normal urine from the same patient was lyophilized. The total solids were 38 grams for the pigmented specimen and 13 grams for the normal. Then 500 mg. of pigmented urine solids were made up to 10 cc using methyl alcohol-hydrochloric acid solvent,

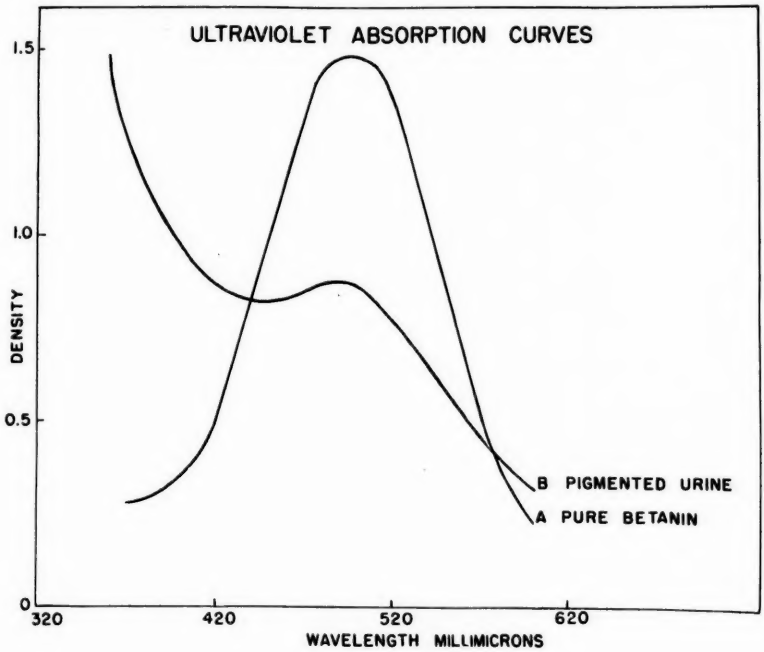

Fig. 1

and 170 mg of normal solids were also made up to 10 cc with the same solvent and used as a blank. Both samples were shaken for ten minutes, and the undissolved solids were permitted to settle out. An ultra-violet absorption curve was run on the clear supernatent.

In Figure 1, Curve A is the absorption curve for the pure beet pigment, betanin; Curve B shows the absorption curve of the pigmented urine. It can be seen that the peaks in curves A and B correspond definitely at about 490 millimicrons. It was therefore concluded spectrographically that the pigment in the urine was the same pigment as that in whole canned beets.

Before any further conclusions were drawn it was felt wise to confirm the fact that controls do not have red pigment in the plasma or urine after massive ingestion of beets. To do this, nine symptomless adult males were selected and instructed to eat a normal supper the night before testing but to avoid alcoholic drinks. They were allowed a glass of water upon rising. They were then fed fifteen small whole

TABLE I.

	Cases	Presenting Symptoms	Clinical Reactions Following Experimental Beet Ingestion									
			Anthocyaninuria	Nasal	Respiratory	Skin	Headache	Gastrointestinal	Ophthalmic	Neuro Muscular	Vascular	Miscellaneous
A. Cases with known anthocyaninuria prior to study but with no known beet allergy	L.D.	Eczema. G.I. Allergy Chronic Fatigue	+			Itching of Neck		Nausea	Burning and Itching of Conjunctivae	Parasthesias of Fingers	Facial Flushing	
	J.G.	Headaches. G.I. Allergy. P.N.A.	+	Nasal Stuffiness				Gaseousness Distention		Fatigue Exhaustion		
	N.P.	Headaches. Allergic Dermatitis. P.N.A. Chronic Fatigue	+	Nasal Stuffiness		Itching of Neck & Arms	Vertex Headache			Nuchal Pain and Stiffness		
	V.B.	Headaches. Nasal Allergy. Chronic Fatigue	+									Chilliness
	R.W.	Headaches. Asthma. P.N.A. Urticaria. G.I. Allergy. Chronic Fatigue	+		Acute Asthmatic Attack		Left Templar Headache					
	R.C.	Headaches. Urticaria. G.I. Allergy. Chronic Fatigue	+	Nasal Stuffiness			Left Hemicrania	"Indigestion"		Nuchal Pain and Stiffness	Facial Flushing	
B. Case of known beet allergy prior to study but never previously aware of anthocyaninuria	L.M.	Parkinson's Disease. G.I. Allergy. Headaches. P.N.A.	+					Nausea Epigastric Distress	Itching of Eyes	Extreme "Dopiness" Nuchal Pain and Stiffness		
C. Case with no previously known anthocyaninuria nor beet sensitivity. Beet test done because of epigastric distress when beets were fed eating tests to other foods	G.M.	Asthma. Hayfever. P.N.A. G.I. Allergy	+			Generalized Itching		Nausea Abdominal Cramps				

D. Cases not aware of beet allergy nor anthocyaninuria prior to study, but showed anthocyaninuria when beets were fed after eating tests to other foods. Subsequently shown to have beet allergy.	J.C.	Headaches. Vertigo. G.I. Allergy. Chronic Fatigue.	+	Acute Rhinitis						Numbness of Arms and Legs		Vertigo
	A.B.	P.N.A. G.I. Allergy. Chronic Fatigue. Ulnar & Sciatic Neuritis	+	Sneezing	Coughing					"Dopiness"		
	H.R	Headache P.N.A. Chronic Fatigue ?Allergic Bladder	+				Generalized Headache	Nausea "Indigestion"		Nuchal Pain and Stiffness		
	S.A.	Severe constant Headaches. G.I. Allergy. Chronic Fatigue.	+									
	O.M.	Hayfever. Chronic Urticaria.	+			Giant Urticaria	Temperal Headache					
E. Case of beet sensitivity suspected on basis of clinical reaction to banana ice cream containing beet sugar.	C.H.	Chronic Eczema. P.N.A. Eneuresis.	+			Itching. Acute Flare of Eczema		Abdominal Cramps				
F. Case of beet allergy diagnosed by anthocyaninuria and clinical reaction after eating test to beets—while being tested as a control.	P.S.	None. Used as control and found to be mildly beet sensitive.	+				Generalized Headache			Nuchal Pain and Stiffness		

TABLE I.—CONTINUED

	Cases	Presenting Symptoms	Clinical Reactions Following Experimental Beet Ingestion									
			Anthocyaninuria	Nasal	Respiratory	Skin	Headache	Gastrointestinal	Ophthalmic	Neuro Muscular	Vascular	Miscellaneous
G. Cases originally without known anthocyaninuria and beet allergy but who developed these symptoms after prolonged and frequent ingestion of beets and beet sugar on elimination diets or rotary diversified diets.	G.A.	Headaches. Nasal Allergy. G. I. Allergy. Chronic Urticaria. Chronic Fatigue.	+	Nasal Stuffiness. Constant Clearing of Throat.						Nuchal Pain & Stiffness. Mental Dullness, Drowsiness		Vertigo Chilliness
	F.A.	Headaches. P.N.A. Myalgias. Chronic Fatigue.	+	Acute Rhinitis			Generalized Headache			Nuchal Pain & Stiffness. Generalized Myalgia. Fatigueand Drowsiness		Chilliness
	H.W.	Eczema, Headaches. P.N.A. Myalgia. Ulnar Neuritis. Intermittent Joint Swelling & Pain. Chronic Fatigue.	+					Nausea. Abdominal Cramps.				
	H.H.	Headaches. Chronic Urticaria. P.N.A. Chronic Fatigue.	+			Generalized Itching.						
	G.G.	Headaches. G.I. Allergy. P.N.A. Myalgia. Chronic Fatigue.	+	Acute Rhinitis				Epigastric Pain		Myalgia Fatigue.		Urinary Frequency
	M.E.B	Headache. Chronic Urticaria Eczema. Chronic Fatigue.	+	Acute Rhinitis	Coughing				Burning Sensation of Eyes.	Drowsiness	Facial Flushing	Chilliness
	F.P.	Chronic Urticaria. Eczema. G.I. Allergy. Chronic Fatigue.	+						Severe Itching Eyes.	Extreme Drowsiness		
	E.B.	Headaches. G.I. Allergy. Chronic Urticaria. P.N.A. Chronic Fatigue.	+					Nausea and Vomiting		Fatigue Exaggerated		Severe Vertigo
	V.M.	Headaches. P.N.A. Chronic Fatigue.	+				Frontal Headache					
	H.B.	Ulcerative Colitis. Headaches. P.N.A.	+					Severe Diarrhea				
	A.S.	G.I. Allergy. P.N.A. Edema of Unexplained Etiology.	+				Generalized Headache			Myalgia		Massive Edema of Left Hand

canned beets. Urine samples were collected before the feedings and at four, eight, and twelve hours after the beet ingestion. Plasma samples were taken before the feedings and at two, four, and eight hour intervals thereafter.

All the urine samples showed a high specific gravity but no evidence of red pigmentation after the test feedings. All the plasma samples were clear of any red pigment. None of these individuals experienced any symptoms after eating the beets. This, we felt, confirmed the observations of Hess and Myers[4] that patients not showing anthocyaninuria reveal no sign of that pigment in the plasma after beet ingestion.

To determine whether beet pigment was excreted in the urine on the basis of a nonspecific allergic reaction in itself or whether it appeared as a manifestation of beet allergy, the following study was undertaken. All new patients under allergic management were asked specifically whether they had ever noted anthocyaninuria and all old patients were similarly questioned. If they had, individual eating tests were done with beets. To ascertain whether beet pigment could be absorbed and excreted as an indicator of a nonspecific allergic reaction in a meal composed of beets and a known reactor, beets were fed routinely after each individual eating test to all other foods. This procedure was carried out by instructing each patient at the completion of an eating test other than to beets to eat one-half of a No. 2 can of whole small beets. They were further instructed to restrict fluids and observe the urine for evidence of red pigmentation. If a patient excreted red pigment in the urine after an eating test to another food such as wheat, after which beets were eaten as outlined above, an eating test to beets alone was then done to determine whether the anthocyaninuria was the result of beet allergy alone or whether the beet pigment appeared in the urine as the result of a nonspecific allergic reaction to a food other than beets. These studies resulted in the observation of twenty-five additional cases of anthocyaninuria. It is felt that the circumstances under which these cases were detected are of considerable interest.

Six cases, LD, JG, NP, VB, RW, and RC, were collected who, in their original clinical histories, stated instances of anthocyaninuria following the ingestion of beets but no known or recognized allergic reaction to them, although they were seeking attention for allergic disease. Table I, Group A, shows the clinical reactions to beets after individual eating tests. Each patient excreted red pigment in the urine after the test feedings.

In Group B, Table I, are listed the clinical reactions following test beet feedings of one case, LM, who gave a history of known beet allergy but was not aware of anthocyaninuria after beet ingestion. Red urine was obtained after this test feeding.

Another patient, GM, reacted clinically to three or four common foods tested but did not have red urine after the ingestion of beets at the com-

pletion of the eating tests to these same common foods. He complained, however, of epigastric distress after beets were fed so that an individual eating test to beets was done on that account. It was suspected that the patient had not restricted fluids sufficiently to concentrate the urine so that the pigment could be recognized or he was not sufficiently observant to notice it. When fluids were restricted and the patient instructed to carefully observe the urine after the beet eating test the anthocyaninuria was then detected. The clinical reactions to the experimental feeding of beets alone are listed under Group C, Table I.

Under Group D, Table I, are listed the clinical reactions of five patients after test feeding to beets. These patients were not aware of having anthocyaninuria after beet ingestion nor were they aware of beet sensitivity. These patients, JC, AB, HR, SA, and OM, all excreted red urine after the test feedings to foods after which beets were subsequently fed. Following this, eating tests to beets revealed the listed symptoms. It will be noted that one patient, SA, showed no clinical reaction, but the fact that she improved clinically when beets and beet sugar were eliminated completely from the diet was taken as probable evidence of beet sensitivity.

Under Group E, Table I, are listed the clinical reactions following experimental beet feedings in one case, CH, a child with eczema, who had a clinical allergic reaction of increased itching after the ingestion of banana ice cream. She had been previously tested to milk, to which she failed to react with the production of symptoms. Bananas had been taken in the diet previously without the production of symptoms, so that beet sugar was suspected since it was one of the ingredients of the ice cream. These observations, and the fact that she excreted red urine after beet test feedings and improved clinically when beets and beet sugar were omitted, were taken as evidence of beet allergy. Subsequently she reacted clinically when beet sugar was again reintroduced into the diet. Beet sugar sensitivity will be discussed further later in this paper.

Another case of beet allergy, PS, Group F, Table I, was diagnosed in one of our office nurses who had no known allergies but gave a history of aversion to beets. We were using her for a normal control when she experienced mild clinical symptoms followed by the detection of anthocyaninuria.

Eleven cases, Group G, Table I, including those of the former control and his wife, were studied in which there had been no previous history of anthocyaninuria nor of beet sensitivity. Four of these patients, HH, MEB, FB, and HB, had been originally fed beets immediately upon completion of individual eating tests to other foods without having noted anthocyaninuria.

Eleven cases, Group G, Table I, including those of the former control and his wife, were studied in which there had been no previous history of anthocyaninuria nor of beet sensitivity. Four of these patients, HH,

MEB, FF, and HB, had been originally fed beets immediately upon completion of individual eating tests to other foods without having noted anthocyaninuria. The other seven had never been fed beets under experimental conditions nor had they previously noted red urine after having eaten beets. The interesting feature in this group is that they had been placed upon elimination diets or rotary diversified diets high in the incidence of beets and beet sugar for various periods of time. Of this group of eleven patients, six, FA, GA, HW, HH, GG, and MEB, had noted clinical reactions in their diet diaries plus the excretion of red urine after having eaten beets. These patients had been on elimination diets containing beets and large quantities of beet sugar. Subsequent eating tests to beets showed clinical reactions as noted in addition to anthocyaninuria.

Five of the eleven patients in this group had been on rotary diversified diets such as described by Rinkel[16] which included the feeding of beets occasionally and the frequent incidence of generous quantities of beet sugar for periods varying from five weeks to two years. Four of these patients, FP, EB, VM, and HB, noted red urine after beets were eaten while on these diets and at the time all were having smoldering allergic symptoms of unknown cause. Individual eating tests to beets were then done, and all showed clinical symptoms listed in Group G, Table I, after the beet feedings. All excreted red urine. Subsequently, when beets and beet sugar were eliminated from the diet their allergic symptoms were relieved. The remaining case, AS, had been on a rotating diet for two years except for the frequent ingestion of beet sugar. She developed chronic allergic symptoms for which no cause could be found; she had never previously reported the excretion of red urine after beet ingestion. An individual food test with beets was done after the avoidance of beets and beet sugar for four days. It resulted in the appearance of the clinical symptoms listed in addition to red urine. Subsequent avoidance of beets and beet sugar resulted in the relief of the chronic allergic symptoms, and the reintroduction of beet sugar into the diet was followed by the reappearance of these same symptoms.

One case, TS, not shown on Table I, is of interest because he is the only case other than the first patient described who excreted red urine coincidentally when beets and a known food reactor were eaten but had neither clinical symptoms nor anthocyaninuria following the ingestion of large quantities of beets alone. Normal compatible leukopenic responses were obtained after eating tests with wheat, corn, and eggs. Beets were fed at the completion of each test without the production of red urine. However, the milk test was followed by the production of a headache and a leukopenic response, and then when beets were fed subsequently the urine contained a red pigment. An individual eating test to beets then failed to produce clinical symptoms or a leukopenic response. The patient did not excrete red pigment when beets were

taken without milk. He refused to co-operate in further studies since he was satisfied that milk was the cause of his headaches.

In an effort to ascertain the incidence of beet sensitivity in this locality among patients studied for major food allergies, seventy-nine patients upon whom individual eating tests were done to foods commonly occurring in the diet were surveyed. These patients had been fed beets after eating tests were completed to other foods. Ten (12.6 per cent) were found to demonstrate anthocyaninuria. These ten patients were studied with individual eating tests to beets and responded with clinical reactions along with the excretion of red urine. Of these ten, five had been previously aware of anthocyaninuria and one of these was aware of beet allergy. Five others had not been previously aware of the excretion of red pigment after eating beets but one of these suspected a beet allergy.

Of these seventy-nine patients, six (7.5 per cent) who had not previously been found to demonstrate anthocyaninuria in the original tests subsequently developed proven beet sensitivity after having been on diets high in the content of beets and beet sugar.

It does not necessarily follow that 12.6 per cent of all allergic patients in this locality demonstrate anthocyaninuria and beet sensitivity, since many allergic patients were seen in whom food sensitivities were of minor importance, or were so obviously sensitive to certain foods that eating tests were not necessary for diagnosis. Furthermore, other patients were seen where the food allergy was of minor severity and the correction of more severe inhalant allergies satisfied the patient. All that can be stated from the figures given are that in food-sensitive patients of a severity necessitating specific diagnosis in the form of individual eating tests, 12.6 per cent were found to be beet sensitive at the onset of the study and another 7.5 per cent developed beet allergy and anthocyaninuria after having been on large quantities of beets and beet sugar in their diets for varied periods of time. While it is appreciated that a difference of opinion may exist as to the need of specific diagnosis for suspected food allergy, nevertheless these figures show that beet sensitivity is a commonly encountered condition. It is admittedly true also that some of these sensitivities were not of a severity necessitating elimination of beet sugar or even beets from the diet.

One wonders whether the allergy to beets may be due to the pigment or beet protein. Efforts to determine this in the two most highly beet-sensitive patients, GA and FA, were inconclusive. Whole beets were treated with concentrated NoOH overnight at a pH of 11. In the morning the pulp was titrated to neutrality with acetic acid. The pigment was thereby destroyed, or at least altered. When the beet pulp so treated was fed to the patients after having avoided beets and beet sugar for four days, they responded with clinical symptoms of nasal stuffiness, headache, and fatigue.

Crude betanin extracted from whole beets was fed in 2 gram doses to

these same patients after another four day elimination of beets and beet sugar. These tests were followed by the production of prompt clinical reactions of headaches and nasal stuffiness. No anthocyaninuria was noted though the stools were subsequently colored red. Why the beet pigment did not appear in the urine of these two patients in the presence of clinical reactions we are unable to explain. We feel that no conclusions can be drawn on the basis of this portion of the study without repeating the experiment repeatedly in the same patients and in others. Furthermore, more purified samples of betanin should have been fed. These studies were not done because of the limited quantity of purified betanin available.

We assume that since these same two patients reacted to beet sugar which is highly refined, it is possible these two patients also reacted to the small quantities of beet antigen in the crude betanin. We can assume that the beet pigment, betanin, was not the antigen the patients reacted to because they reacted to the beet pulp in which the betanin was previously destroyed or altered. On the other hand, it is also conceivable that the beet protein also could have been altered at the pH of 11. Our opinion, on the basis of these studies, is that the sensitivity is more likely to beet protein rather than the pigment because the pigment is highly unstable. The combined sensitivity to both the pigment, or its altered fractions, and the beet antigen, or its altered fractions, still remains a remote possibility.

Included in this series of twenty-eight cases presented we have observed five, GA, FA, GG, CH, and AS, in whom we were able to convince ourselves without question of doubt that beet sugar produced a cause and effect relationship between ingestion and the production of allergic symptoms. We obtained individual eating tests to beet sugar in three of these cases, FA, GA, and GG. One complained of frontal headache with nuchal pain, another rhinitis, generalized muscle aching and epigastric pain, and the last nasal stuffiness and severe itching of the nose. The fourth case, CH, who reacted to banana ice cream, has already been described. The fifth case, AS, with smoldering symptoms relieved by the avoidance of beets and beet sugar and reproduced by the reintroduction of beet sugar into the diet, has also been discussed.

Duke[2] in 1926 described the first case of sensitivity to beet sugar. The possibility of sensitivity to refined sugar at first seemed incredible to us, but the report of corn sugar sensitivity by Randolph and Yeager[11] and Randolph, Rollins and Walter[12] lent credence to this possibility. Furthermore, the report of cane sensitivity by Randolph and Rollins[13] and their subsequent observations of beet sugar sensitivity[14] support our findings.

DISCUSSION

It is difficult to answer the question of why patients who were proven to demonstrate anthocyaninuria after experimental testing were not aware

of the fact that they had previously exhibited this phenomenon. In the first place, individuals eating beets have red stools, and when the patient is a female, no observation is usually made of the urine unless it is collected in a vessel separately. On the other hand, it is of interest that even in the male, red pigment was not previously noted prior to testing. The only answer to this question is that either the patient's attention was not too closely drawn to the color of the urine though it might have been pigmented, or the fluids were not restricted sufficiently after ingestion, or an insufficient amount of beets were ingested to pigment the urine deeply enough so that visible pigmentation could be noted. It should be emphasized here that unless sufficient beets are ingested and unless fluids are restricted following ingestion, the urine may be slightly pigmented an orange color. This can escape detection unless particular attention is paid in observing the color of the urine.

On the basis of the evidence presented, it would seem that in the patient who has developed an allergy to beets, the gastrointestinal tract allows access of the beet pigment into the blood stream from which it is excreted by the kidney. It was originally felt that beet pigment might be used as an indicator in the urine for reactions to other foods. This has not proven to be the case though we are unable to explain why it apparently did so in two of the cases presented. Whether other pigments or dyes may be found to act in this fashion seems worthy of investigation.

Of interest particularly are the eleven patients who were previously not beet sensitive or possibly mildly so, who later developed a definite proven beet allergy on diets high in the incidence of beets and beet sugar and then were able to excrete red pigment in the urine after beet ingestion concurrent with clinical allergic reaction to the beets. If this is the case, it would seem wise to be cautious in the case of allergic patients so that sensitivity may not actually be induced by a diet where this food is urged in generous quantities.

We feel that on the basis of this study it is important to suspect beet allergy where red urine is found after beet ingestion, and in the instances where one is searching for the cause of chronic symptoms, beet allergy should be suspected and beets and beet sugar omitted from the diet for a trial diagnostic period. This is particularly true in areas where the sugar available is largely from beets.

The criterion for the diagnosis of beet sensitivity in this paper has been the production of clinical symptoms after the experimental feeding of beets to patients having previously avoided beets and beet sugar for four days. The test feedings were on the fifth day. We have accepted anthocyaninuria as a valuable aid in the diagnosis of beet allergy. As a rule, leukopenia in the serial white blood cell counts of the individual eating tests to beets showed a high degree of correlation with the clinical reactions. Many of the beet sensitive patients found it was not nec-

essary to eliminate beet sugar from their diets. These patients usually avoided beets as such voluntarily as a result of the clinical tests.

We have studied three patients in whom we felt we were able to produce allergic reactions after test feedings of beets but have as yet been unable to produce anthocyaninuria. These patients, normal in other respects other than their allergic state, all were subjected to a thorough clinical study. No explanation can be made as to why they did not excrete the red pigment even though beets were eaten in large quantities.

CONCLUSIONS

1. Twenty-eight cases of anthocyaninuria are presented. Twenty-six are related to beet allergy, and two seem related to the ingestion of beets along with foods known to have produced allergic reactions.

2. Three patients have been studied in whom clinical reactions are obtained when beets are fed experimentally but no anthocyaninuria detected.

3. Anthocyaninuria seems dependent upon the absorption into the blood stream of the pigment from the intestinal tract during the allergic reaction; it is then excreted by the kidney into the urine. Normal individuals do not absorb detectable quantities of betanin from the intestinal tract.

4. Anthocyaninuria is a valuable sign in the diagnosis of beet allergy.

5. Caution is warranted lest beet sensitivity may be produced in the highly food-sensitive patient by the too frequent and copious feeding of beets and beet sugar.

6. Five cases of beet sugar sensitivity are herein reported.

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REFERENCES

1. Cathala, J.; Martrou, P., and Gras, L.: Sur le passage du pigment de la betterave rouge dans les urines. Bull. Soc. Pediat. de Paris, 37:88, 1939.
2. Duke, W. W.: Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy. St. Louis: C. V. Mosby Co., 1926.
3. Halle, J., and Girard, L.: Passage du pigment de la betterave rouge dans l'urine de l'enfant. Bull. Soc. Pediat. de Paris, 36:266, 1938.
4. Hess, A. F., and Myers, V. C.: Carotinemia. A new clinical picture. J.A.M.A., 73:1743, 1919.
5. Horwitt, M. K.: Observations on behavior of anthocyan pigment from Concord grapes in animal body. Proc. Soc. Exper. Biol. & Med., 30:949, 1933.
6. Jervis, J. J.: Acidosis and hepatic disorders. Brit. M. J., 1:1408, 1914.
7. Matheson, A.: Anthocyaninuria. Am. J. Dis. Child., 51:226, 1936.
8. Poole, M. W.: Anthocyaninuria. Am. J. Dis. Child., 33:784, 1927.
9. Pulcher, G. W.; Curtis, L. D., and Vickery, H. B.: The red pigment of the root of the beet. I. The preparation of betanin. J. Biol. Chem., 123:61, 1938.
10. Randolph, T. G., and Rawling, F. A.: Blood studies in allergy. V. Variations in total leukocytes following test feeding of foods. An appraisal of the individual food test. Ann. Allergy, 4:163, 1946.
11. Randolph, T. G., and Yeager, L. B.: Corn sugar as an allergen. Ann. Allergy, 7:651, 1949.

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BRONCHIAL ASTHMA IN SMALL COMMUNITY HOSPITALS
Five-Year Survey

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THE purpose of this survey is threefold:

First, it presents a statistical analysis of all the bronchial asthma cases coming under hospital treatment in a midwest industrial city of about 50,000 population.

Second, it offers a cross-section of the type of history, diagnosis and treatment by general practitioners in any American community of about the same size and location.

Third, it suggests some improvements in the handling of bronchial asthma.

This review is not intended as a criticism of anyone or any group of physicians or of hospital management *per se*, but rather as a factual study of a group of 157 cases diagnosed as "bronchial asthma" with the thought that the shortcomings revealed may be corrected. The cases were treated by twenty-six general practitioners, all graduates of Class A medical colleges, and with the usual one to two years of internship training plus some years of experience in practice. The two hospitals from which the records were analyzed are 125-bed and 75-bed institutions respectively, and are accredited by the American Hospital Association and the American College of Surgeons. The doctors are all staff members of both hospitals. I have carefully scrutinized and dissected every one of these 157 case histories (of which forty-one are my own) and set down the statistical data in the following break-down charts. This survey, therefore, is a fair index of the type of treatment probably found in any city of like size and location with the possible exception of research medical centers.

Dr. Leon Unger, in his recent book "Bronchial Asthma," defines this disease complex as "an allergic condition characterized by wheezing, dyspnea, orthopnea, and cough, and often associated with rhinitis and with the partial obstruction of the lower air passages."

With this definition of asthma in view, we consider how these postulates have been followed in the present survey of 157 case histories from the Kenosha Hospitals. Of these, sixty-nine were males and eighty-eight females. They were all of the Caucasian race. The ages ranged from eight months to eighty-four years (Table I). The duration varied from three attacks (in two months) in an eight-month-old infant to numerous attacks over an interval of thirty-five years in a male of seventy-five. The average duration for the group was 7.1 years. The etiology was

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undetermined in eighty-seven; allergenic in seventy; and sixteen had associated cardiac disease (and so-called cardiac asthma (Table II). Classified according to type (Unger classification), there were forty chronic cases, eighty paroxysmal cases, and thirty-seven cases of undetermined classification (Table III). In only eighteen cases was there any

TABLE I.
TOTAL NUMBER OF PATIENTS

Age	Sex		Total
	M	F	
0 to 10	8	6	14
10 to 20	8	10	18
20 to 30	5	10	15
30 to 40	17	8	25
40 to 50	5	19	24
50 and over	26	35	61
	69	88	157

Family histories: 18.

TABLE II. DURATION OF ASTHMA
Average for all—7.1 years

Age	No. Yrs.	Average
0 to 1 year	1	.31 years
1 to 10	14	.662
10 to 20	18	4.8
20 to 30	15	5.1
30 to 40	25	5.35
40 to 50	24	7.7
50 and over	61	11.39

TABLE III. ETIOLOGY

Undetermined	Allergenic		Associated Heart Disease
87	45		16
	Dust, Pollens, Epidermals, Feathers, Foods	45	
	"Colds"	25	

TYPE OF ASTHMA—
UNGER CLASSIFICATION

Chronic	Questionable	Paroxysmal
40	37	80

Family histories: 18.

TABLE IV. SYMPTOMS AND PHYSICAL FINDINGS

Symptoms	
Dyspnea	97
Cough	132
Wheezing	131
Orthopnea	27
Fever	13
Associated Rhinitis	5
Abdominal Pain	6
Vomiting	3
Weakness	6
Pain in chest	3
Important Physical Findings	
Râles	113
Cyanosis	15
Emphysema	18
Hyperresonance	9
Prolonged Expiration	9
Tachycardia	2
Ascites	2
Edema of legs	2
Associated Eczema	1
Nasal Polyps	2
Enlarged Cardia	4

family history obtained. The cardinal symptoms of wheezing, dyspnea, cough and orthopnea were listed in a majority of cases, but not in all cases (Table IV). The physical findings were not always listed in the histories, but as nearly as I could determine they are set forth in Table IV. Associated rhinitis was listed in only five cases.

Laboratory studies of this series are listed as is the study of the eosinophile counts of the blood (Table V). The paucity of proper allergic studies (only forty-five of 157 cases) and of eosinophile counts (only forty-three) are also noted; only 10 sputum and nasal smears were done. X-ray examinations were made in only fourteen cases (less than 10 per cent). The x-ray diagnoses made by the roentgenologist are listed in Table VI.

Treatments (Tables VII, VIII and IX) varied from narcotics—morphine, pantopon, codeine, dilaudid, demerol and papaverine in 100 cases to epinephrine in ninety-four cases, aminophyllin in sixty-eight cases, oxygen in sixty-two cases, barbiturates in forty-one cases, iodides in

TABLE V. LARORATORY STATISTICS

Allergic study	45
Blood Smears for Eosinophiles	43
Sputum and nasal smears	10

TABLE VI. X-RAY DIAGNOSIS

Peribronchitis	3
Peribronchitis and Bronchiectasis	1
Subacute Bronchitis	1
Peribronchial Fibrosis	2
Chronic Bronchitis	3
Broncho-Pneumonia	2
Lobar Pneumonia	7
Dissecting Aneurysm	1
Total	14

TABLE VII. TREATMENT CHART

Drug	Number Patients Treated	Results			
		Good	Fair	Poor	Death
Morphine	19	5	4	7	3
Pantopon	46	16	16	7	5
Demerol	20	7	8	5	0
Codiene	10	5	3	2	0
Dilaudid	2			1	1
Papaverine Hcl	3		2	1	0

TABLE VIII. TREATMENT CHART

Drug	Number Patients Treated	Results			
		Good	Fair	Poor	Death
Epinephrin	94	53	25	6	1
Aminophyllin	68	52	16	6	0
Oxygen	62	36	11	7	4
Antihistemines	23	8	7	5	0
Iodides	15	5	5	4	1
Ephedrine	20	12	3	3	2
Penicillin	30	18	6	5	4
Sulfonamides	6	3	2		1

fifteen cases, digitalis preparations in thirteen cases, penicillin in thirty cases, the antihistiminics in twenty-three cases and isuprel in five cases. The large number of cases treated with the various narcotics is particularly noteworthy, and it is interesting to note that the largest number of deaths (nine) occurred in those patients receiving morphine, pantopon and dilaudid particularly. Also, the poorest results occurred in those cases receiving narcotics, although the lack of serious complications was not noted in a majority of these cases. The large percentage of deaths in the narcotic-treated cases of asthma, as well as the poor response to treatment, coincides with and bears out the views of the leading authorities, who decry the use of narcotics in bronchial asthma.

The results of treatment (Table X) show that the average hospital stay was 6.16 days and varied from 2.1 days in the infant to 10.65 days in the fifty-year and over age group of patients. It also shows that the most rapid improvement occurred in the younger age groups. In nearly

TABLE IX. TREATMENT CHART

Drug	Number Patients Treated	Results			
		Good	Fair	Poor	Death
Phenobarbital	21	15	3	3	0
Nembutal	10	4	4	1	1
Seconal	9	4	3	1	1
Digitalis	13	3	4	3	3
Calcium Gluconate	8	3	2	3	
Isuprel	5	3	2		
Tedral	5	1	4		
Thiamin Chloride	2		1	1	

TABLE X.

Age	Days of Hospital Stay	Degree of Relief			
		Good	Fair	Poor	Death
0 to 1	2.1				1
1 to 10	2.65	11	2		1
10 to 20	5.25	13	4	1	0
20 to 30	6.65	12	2	1	0
30 to 40	8.81	16	6	2	1
40 to 50	8.20	14	6	3	1
50 and over	10.65	15	21	16	9
Averages	6.16	81	41	23	12

every case, several drugs were used and are listed. In many cases, it was difficult to determine which drug gave the primary degree of relief. However, the various drugs and the doses of each were carefully studied in each case and where one particular drug was used most frequently and the response to it was recorded, such drug was considered the primary one in that instance and it was so listed. It will be noted that the greatest relief occurred first with aminophyllin where out of sixty-eight cases fifty-two obtained good relief, sixteen fair and six poor. Next came epinephrine with which fifty-three of ninety-four cases obtained good relief, twenty-five fair, and six poor, and there was one death. Third came oxygen where out of sixty-two cases thirty-six obtained good relief, eleven fair, seven poor and there were four deaths. It must be mentioned that in practically all of these deaths where oxygen was the primary treatment, the patients had previously had other treatments and were *in extremis* on entrance into the hospitals.

The above survey suggests the need of the great improvement in both diagnosis and treatment of bronchial asthma by general practitioners, namely:

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FURTHER STUDIES ON THE USE OF TISSUE CULTURE OF BLOOD LEUKOCYTES IN THE CLINICAL EVALUATION OF BACTERIAL HYPERSENSITIVITY OF THE TUBERCULIN TYPE

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THIS STUDY concerns a slightly different means of determining sensitivity to specific bacterial strains and, in consequence, a slightly different method of treatment. It follows along lines laid down years ago by Rich and Lewis,[4] Moen,[3] Aronson,[1] Heilman, Feldman and Mann.[2] In their work on animals, they showed that cells, taken *in vitro* from animals sensitized to tuberculin, became necrotic when subjected to tuberculin, while cells from healthy animals were unaffected. In their experiments, they used both blood leukocytes and the spleen of animals for their tissue cultures.

The present study differs in that only blood leukocytes were used and not those from animals but from man. It also differs in that the matrix used to hold the cells in contact with the bacterial filtrate during the test, was fibrinogen and thrombin instead of plasma. Plasma was naturally tried first, but it was found that the antibodies in the plasma interfered with the action of the filtrate on the leukocytes. After a number of experiments, fibrinogen and thrombin was found to eliminate this difficulty.

In previous studies, cytotoxic indices had been used for measuring the extent to which leukocytes had been inhibited from migrating. By using fibrinogen, however, which has less extraneous material, we could determine necrosis directly.

PROCEDURE FOR OBTAINING LEUKOCYTE SUSPENSION

The citrated venous blood was first centrifuged and the plasma layer so removed that the layer of leukocytes beneath was not disturbed. The leukocytes were then coagulated into a Buffy coat by carefully overlaying them with a layer of calcium Ringer's solution, pipetting off the Ringer's solution, overlaying fresh calcium Ringer's solution and pipetting this off, then overlaying the leukocytes a third time with calcium Ringer's solution and taking it off also. By this time the leukocytes had adhered together sufficiently for the whole layer to hold together while being picked off the layer of red cells.

To dispose of the red cells which clung to the bottom of the Buffy coat, it was laid in a petri dish containing simple Ringer's solution. With a trabismus hook the red cells were teased away from the Buffy coat. A second or even a third petri dish of Ringer's solution was used to get the Buffy coat reasonably clean.

The Buffy coat was then lifted out and shredded in a Petri dish. The

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shreds were dropped into a bottle containing 3 cc of Ringer's solution, and incubated approximately an hour. During this time such numbers of the leukocytes migrated well up and throughout the Ringer's solution as to form a dense suspension of cells.

DESCRIPTION OF EACH TISSUE CULTURE TEST FOR SENSITIVITY

Ordinary glass slides were prepared with rings or well-walls of vaseline, one for each bacterial filtrate for which a test was to be made. Into each ring, or well, was dropped one drop of full strength thrombin, one drop of cell suspension, and then three drops of the filtrate for which this test was being made. This should have filled the ring to overflowing. The mixture was then sealed in by easing a coverslip atop the vaseline ring, and put to incubate for eighteen hours at 37° C.

Normally, leukocyte cells remain viable for approximately thirty-six hours. Thus, at the end of the eighteen-hour incubation with the filtrate, the cells should, naturally, still be viable. However, many cells of certain individuals had become granular, stippled, crenated or even died out completely in the tests for certain of the filtrates. These individuals, then, were bacterially sensitive, but only to such strains as caused necrosis of their white cells. If no strain caused necrosis, the individual was not sensitive—in other words, normal.

TESTS OF SENSITIVITY TO VARIOUS ANTIGENS

Using this same procedure, leukocytes taken from patients suffering from atopic hypersensitivity were found unaffected by the atopic allergens. This confirmed previous findings.

A reagin containing plasma from patients with atopic sensitivity also, and naturally, had no effect upon leukocytes. Tissue culture studies by other investigators had reported that toxins had no effect. These findings, too, were confirmed.

Histamine in high concentration was also found not to affect the viability of cells.

Diphtheria toxins from two different sources* were used in concentrations as high as 125 to 7000 MLD per c.c., but no necrosis whatsoever was found. Toxins strong enough to kill a guinea pig had no effect upon the leukocytes *in vitro*. In short, necrosis is caused by bacterial filtrates but not pure toxin.

For practical reasons, particular attention was paid to the hemolytic streptococci Group A of Lancefield's classification. Originally, thirty strains were used in the battery of tests for each individual. Now forty-two are used, but this report concerns the tests on only those original thirty.

*The authors gratefully acknowledge the generosity of the Massachusetts Department of Public Health Division of Biologic Laboratories, and the Lederle Laboratories for supplying the diphtheria toxin.

RESULTS

An analysis of test results was made to discover whether certain strains caused necrosis more often and, if so, which. Two thousand tests were run with Group A hemolytic streptococci strains, of which 213 became necrotic, or were positive. Some strains caused necrosis in as many as twenty-one cases, others in only one or two. There was apparently considerable cross reactivity.

Few patients were positive to only one strain, most to two or three. Frequently, these were relatively unrelated in a serological sense. For this reason, Lancefield's classification on a serological basis ultimately may not be the one to be used. It may be the colony form which is important. An investigation is contemplated to determine which means of differentiating bacteria is most effective.

The blood of 300 patients was tested by a battery of 30 Group A hemolytic streptococci and 70 other bacterial filtrates.

Patients positive to different group A	
hemolytic streptococci	213
to different Streptococcus viridans strains	60
to different Staphylococcus aureus strains	56
to different Staphylococcus albus strains	42
to different pneumococcus strains types 1 to 14, and	21
to various other strains	30

To check the accuracy of each test to a given filtrate, a duplicate test was run with blood drawn on a second day. All tests found positive were run a third time. Only those tests which were consistently positive were termed positive, all others were considered negative.

An overall check was made to ascertain the accuracy of the 2,000 tests. Each test was duplicated, and a correlation of 81.8% was found between the two runs. Ten per cent of this "error" can be accounted for by the fact that sterility tests showed an error of 10 per cent. Airborne contamination, especially by molds, is almost impossible to prevent entirely.

DESENSITIZATION OF PATIENTS

Zinnser and Grinnell found that bacterial filtrates were most effective in eliciting skin reactions in sensitized animals and that, in skin testing, these filtrates were more reactive than nucleoproteins or whole dead organisms. It would follow, then, that the same broth filtrates should be used in desensitizing the patient as had been used in the tissue culture test which established his sensitivity.

Of the first 158 patients considered positive, 102 were or are being desensitized. To desensitize a patient, a mixture was made of the filtrates to which he had been found sensitive. Dilutions were prepared starting with 1:1,000,000 and increasing in concentration to 1:100,000, 1:10,000, 1:1,000, 1:100, 1:10 and sometimes full strength.

Before beginning the program of desensitization, a skin test was made on the patient using 1/20 cc of the 1:1,000,000 dilution. Subsequent inoculations, made every three or four days, were increased by 0.1 cc each time—provided there were no reactions. Whenever a reaction occurred, the dosage was repeated until it was well tolerated. Then it was increased again.

Reactions were usually mild and could be classified as local, focal or general. Of the fifty-eight patients then under treatment, eight had general reactions, thirteen focal or general reactions, thirty focal reactions, four local, and two local and focal. The general reactions were febrile, often preceded by a chill. Most reactions occurred early in the course of desensitization, and it was interesting to note that the type of reaction remained constant for each individual patient regardless of the dosage responsible.

Thirty-six patients who were apparently clinically cured, and were down to 1:10 dilution, had their tissue culture tests for sensitivity repeated in duplicate. Of these, thirty-three had then only negative tests; three patients who had been originally positive to several different strains were then negative to all but one strain.

A great variety of initial diagnoses were among those patients tested and treated. Among them were asthma, infectious arthritis, rheumatic fever, rheumatic fever with arthritis, sinusitis, sinusitis with asthma, allergic rhinitis, bacterial-type, recurrent iritis and arthritis, periarteritis nodosa, Christian Schueler disease, and chronic "id" infections.

Characteristic of all patients, a number of those used in this investigation became discouraged before an adequate program of desensitization could be completed. Of 158, fifty-six dropped out. Of the 102 who either completed their program or were still under treatment, not all, six, in fact, had shown no signs of sustained improvement. That, of course, could have been due to either a fallacy in the theory, or to the fact that, though approximately 100 different strains of bacteria were included in the battery of tests, this is but a fraction of the total number to which patients reasonably could be assumed to be sensitive.

It is to be remembered in this regard that patients test positively to more than one strain, rarely to only one. It is therefore possible that, though they were positive to two or three of the strains in the battery, they were positive also to two or three strains for which no tests were made. The very gratifying results obtained, however, with those patients who did complete their series of desensitization inoculations and responded is indicative that further studies along these lines should be made. Of the 102 patients, only six did not improve or only partially improved, but ninety-six lost all their initial symptoms.

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PYROMEN IN THE TREATMENT OF PERENNIAL ALLERGIC SYMPTOMS

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INTEREST in the possible therapeutic value of Pyromen arose from the observation that patients developing constitutional symptoms from the administration of intravenous fluids appeared to obtain some therapeutic benefit as a result of those reactions.[10] Since pyrogen contamination is the most common cause of chills and fever following venoclysis and since fever therapy has long been recognized as having therapeutic value, an effort was made to isolate the material responsible for these reactions. This led to the eventual preparation and standardization of Pyromen. As a consequence of this effort the pharmacology of Pyromen has been carefully studied for the past several years.

Extensive laboratory[2,40-42] and clinical investigations[8,9,11,12,38] of Pyromen have demonstrated that it is virtually non-toxic and non-anaphylactogenic and may be employed safely within a wide range of dosage. Early clinical studies in neurosyphilis by Lonson and Liebert,[9] in malignant hypertension by Page and Taylor[11] and in dermatologic conditions by Kierland and Kulwin[8] demonstrated the relative safety of this preparation in the treatment of human illnesses. It should be pointed out, however, that these early clinical investigations were concerned with the use of Pyromen only as a readily controlled pyrogenic agent.

The technique for the detection of bacterial pyrogens as well as that employed for the standardization of Pyromen depends upon the development of a characteristic febrile response following intravenous injection in test animals. This mode of administration in animals is also associated with a blood response consisting of an initial diminution of the total leukocytes and a delayed leukocytosis. The initial leukopenia is characterized by a reduction in number of all white blood cells. The subsequent leukocytosis consists principally of myeloid elements and develops in the presence of a sustained lymphopenia and eosinopenia.[20] Identical variations in the cellular elements occur when Pyromen is injected intravenously in man. The similarity of this blood response following an intravenous injection of Pyromen to that following the experimental ingestion of an allergenic food[17,18] or drug[16] in specifically sensitized allergic patients and to the blood response following the administration of adrenocorticotropic hormone (ACTH) in animals[4] and human beings,[7,22,26] and the fact that ACTH is effective in the therapy of allergic diseases[1,26,34] suggested the use of Pyromen in allergy.

Initial observations in allergy patients were made employing Pyromen

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Pyromen was supplied through the courtesy of Dr. N. M. Nesset, Baxter Laboratories, Inc., Morton Grove, Illinois.

in relatively large intravenous doses in an effort to obtain febrile responses between 101 and 104 degrees. Although treatment at a level to accomplish this end impressed us with the therapeutic value of this preparation, the severity of the chills, muscle aching, and fever and the fact that allergic symptoms were sometimes temporarily accentuated following such doses limited its usefulness in the treatment of asthma, dermatitis, and other allergic syndromes. With additional experience it became apparent that a more satisfactory clinical response may be obtained as a result of small doses either not associated with the precipitation of such constitutional symptoms or followed by the development of mild chilling or muscle aching. This preliminary report deals with observations on 150 patients with various allergic syndromes treated with Pyromen since October 1, 1949. The duration of therapy has ranged from ten days to eight months.

THE INTRAVENOUS ADMINISTRATION OF SMALL DOSES OF PYROMEN

The dosage schedule found to be most satisfactory in the treatment of allergic conditions is as follows: 1.0 or 2.0 gamma (micrograms) of Pyromen, diluted in saline to permit accurate measurement, is given as the initial intravenous dose. This may be followed in one to four hours by transient chills or chilliness and is not usually associated with a subsequent febrile response. The simultaneous administration of 0.65 grams of acetylsalicylic acid (providing the patient is not specifically sensitive thereto) often prevents the development of distressing symptoms. In the event that annoying chilling or muscle drawing develops, additional aspirin or the ingestion of approximately a tablespoonful of sugar effectively reduces these symptoms.

A dose of Pyromen that is followed by a chilling response is usually associated with an initial leukopenia followed by a leukocytosis, characterized by a shift to the left of the myeloid elements. There is a coincident lymphopenia and eosinopenia. That this response is not entirely correlated with the production of constitutional symptoms is due to the fact that a similar blood pattern also develops with a slightly smaller dose insufficient to produce such symptoms. A characteristic blood response from the intravenous injection of 5 gamma (micrograms) of Pyromen is shown in Figure 1. It will be noted that in general this is similar to the hematologic response following the administration of ACTH or Cortisone.

The initial intravenous injection of Pyromen is most commonly associated with an improvement in allergic symptoms for a period of twelve to eighteen hours; it may or may not be followed by chilling and other symptoms of reaction. A second dose is usually given forty-eight hours after the first injection, which in turn, is commonly followed by some amelioration of allergic symptoms for a period of forty-eight to seventy-two hours. A third injection is given at the termination of the period

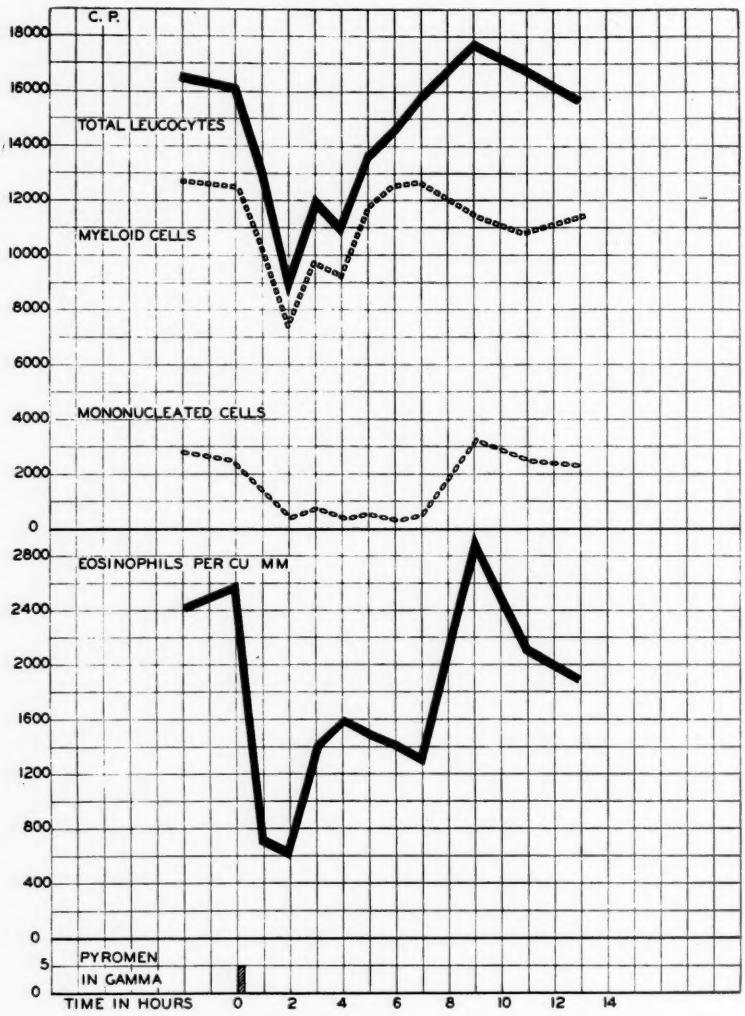

Fig. 1. A characteristic blood response following a single intravenous injection of Pyromen in C. P., a patient with a diagnosis of severe bronchial asthma and allergic rhinitis with nasal polypi.

of effectiveness following the second dose, the interval between these doses usually varying between three and seven days. Fourth and subsequent intravenous injections are administered as often as necessary in order to perpetuate the degree of improvement previously attained. The interval between injections at this stage of therapy usually varies from three days to three weeks, depending somewhat upon the allergic

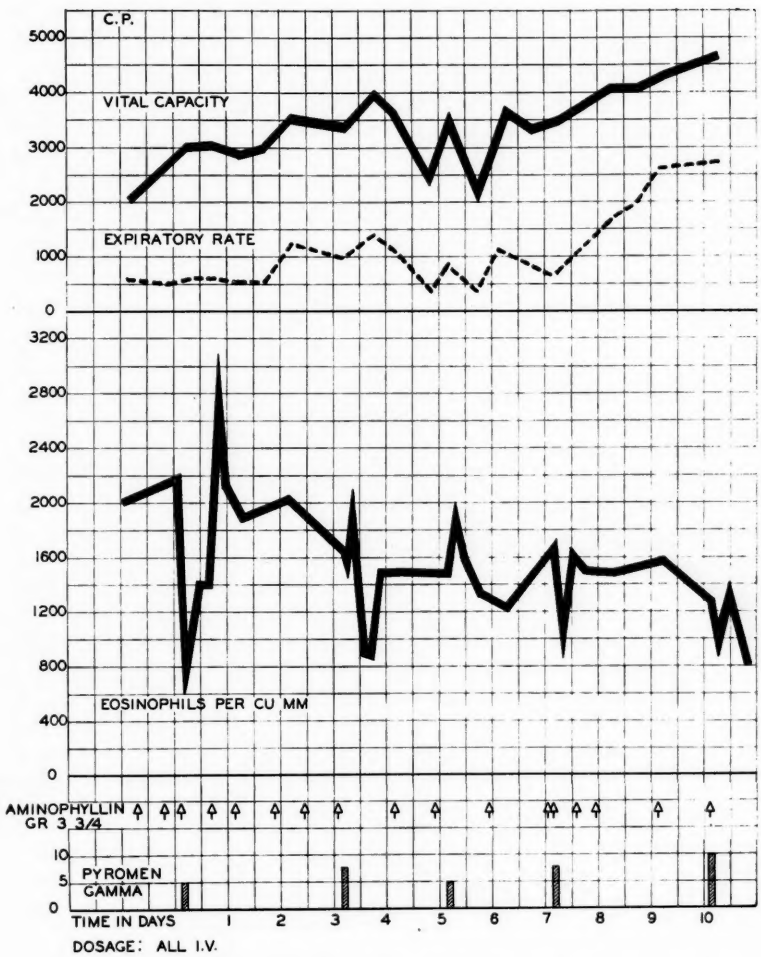

Fig. 2. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils following a series of intravenous injections of Pyromen in C. P., a patient with severe bronchial asthma and allergic rhinitis with nasal polypi. Similar observations following treatment with ACTH,[13,26] Cortisone[21] and Concentrated Adrenal Cortex Extract[19] have previously been reported.

manifestation being treated and the individual's specific allergic diagnosis and degree of allergic control. Exceptions to this schedule have been observed in some children in whom beneficial effects may persist for as long as three months. In general, the dosage requirements for children over the age of three years are essentially the same as for adults. Children tolerate the drug well and frequently respond more satisfactorily than adults.

Variations in the clinical response and level of circulating eosinophils following treatment with repeated intravenous doses of Pyromen is shown in Figure 2; this is the same patient whose blood response following a single intravenous dose was previously illustrated.

In the event the initial intravenous dose is not followed by evidence of clinical improvement, the expected blood response, or by the development of a mild constitutional reaction, a second intravenous dose approximately 50 per cent greater is given at the end of forty-eight hours. Subsequent doses employing the same increment and interval are continued until one or more of the above manifestations of a satisfactory therapeutic response are attained. When an effective dosage level is reached, one determines the duration of the period of clinical improvement by awaiting the recurrence of the former symptoms. If this period of improvement is four days in duration or less, one repeats the former amount in subsequent doses. If this period of improvement exceeds four days in duration and particularly if it exceeds a week, a constitutional reaction may often be avoided by giving a dose 25 per cent smaller than the amount previously administered. This level and interval of dosage may be continued until constitutional reactions occur or until it becomes ineffective; the dosage is then decreased or increased slightly according to the indications. It is sometimes necessary to make several successive step-wise reductions in the dosage in specifically diagnosed allergic patients receiving long-term intravenous therapy, examples of which are illustrated in the upper part of Figure 3. Others, particularly if relatively uncontrolled from the specific allergic standpoint, may often be retained at a constant level or may require a slight increase in dosage; the latter type is illustrated in the lower part of Fig. 3.

Except for patients with specifically undiagnosed dermatitis or bronchial asthma, who appear to require somewhat larger doses, most allergic individuals have been treated within a dosage range of 0.5 to 10.0 gamma (micrograms).

THE ORAL ADMINISTRATION OF PYROMEN

It would appear that Pyromen is absorbed through the buccal mucosa as judged by the development of clinical improvement, the previously described type of blood response, and constitutional reactions following the sublingual use of this preparation. The technique employed is to allow a saline dilution (5 gamma per cubic centimeter) of the material to remain in contact with the buccal mucosa for a period of at least five minutes before swallowing.

In general, a less striking variation in the cellular elements is observed as a result of oral therapy than following the intravenous administration of Pyromen. Comparative blood responses in the same patient are shown in Figures 4 and 5.

The constitutional reactions following oral therapy of Pyromen are

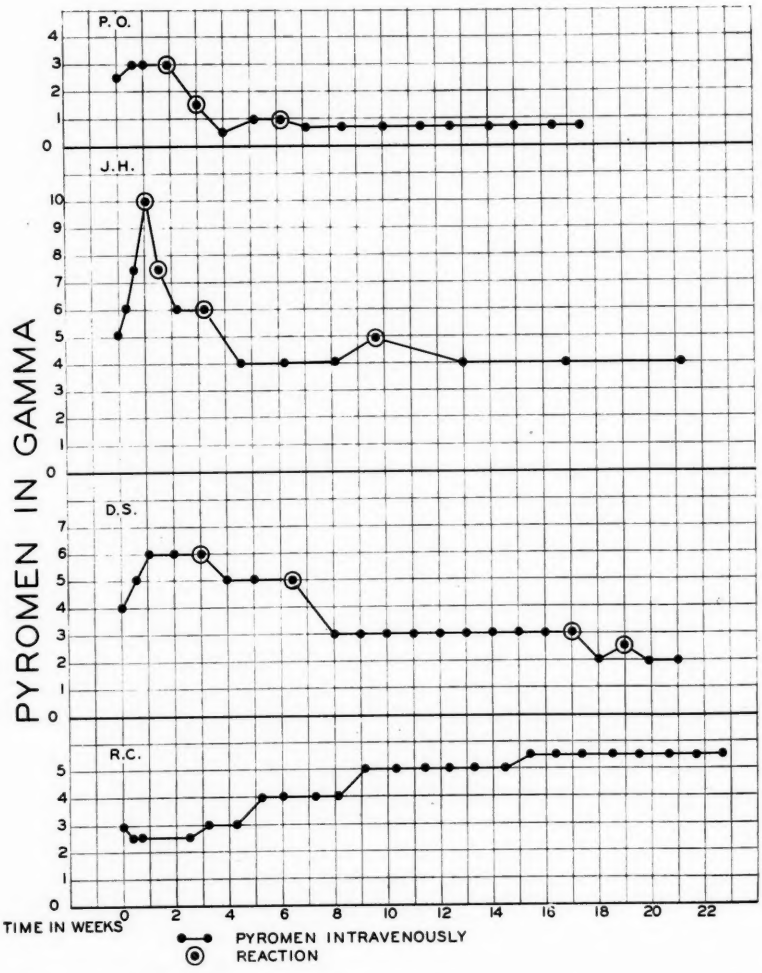

Fig. 3. Illustrative dosage schedules in patients receiving intravenous Pyromen therapy. The first three allergy patients had clinical improvement after the initial intravenous doses shown above but then developed constitutional reactions as indicated by the circles. The subsequent reduced dosages were tolerated and maintained satisfactory clinical improvement. The fourth patient has required a gradually increasing dosage schedule to maintain improvement of her symptoms.

more delayed in onset and less severe than those associated with the intravenous route of administration. The mildest type of constitutional response observed consists of fatigue, irritability, and listlessness developing as late as seventy-two hours after the buccal administration of the drug. This type of response may readily be overlooked unless one is aware of its possible development. With larger doses the reaction

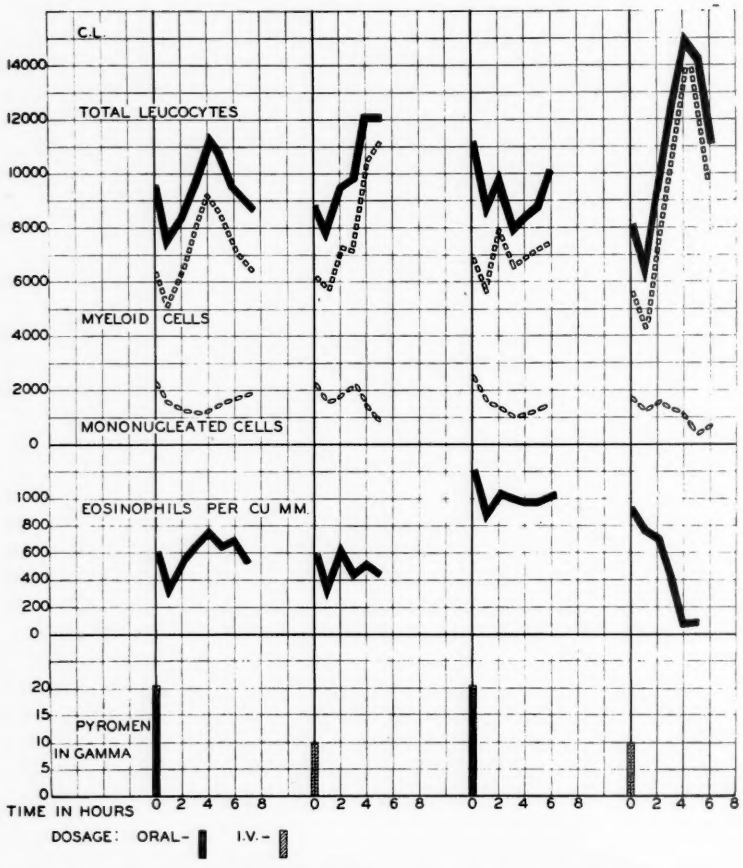

Fig. 4. C. L., a patient with allergic rhinitis, myalgia, and fatigue, had temporary improvement in symptoms following each oral or intravenous dose of Pyromen. Variations in the total leukocytes, myeloid, mononucleated and eosinophilic cells following the alternate administration of Pyromen by the oral and intravenous route are illustrated.

may be expected to come on more rapidly and is usually associated with the additional symptoms of muscle aching and drawing sensations.

Initial attempts to obtain a satisfactory therapeutic response in allergic disease as a result of administering Pyromen only by the oral route have thus far been relatively unsuccessful, although this has been accomplished in several children and occasionally in adults. The oral route of administration has been most helpful when combined with intravenous therapy. A workable joint program consists in giving two to four intravenous doses as previously outlined, following which clinical improvement may usually be maintained as a result of oral therapy. The amount given orally is usually identical or 50 per cent greater than the amount

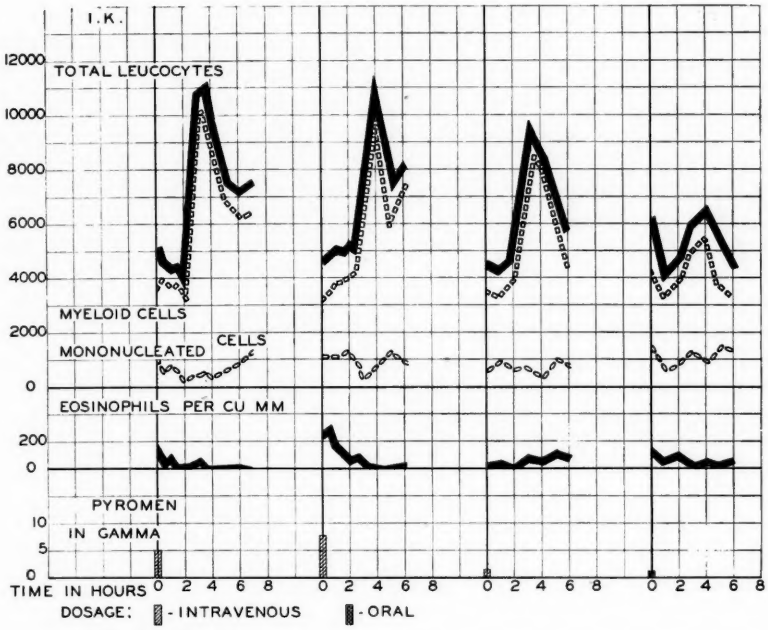

Fig. 5. I. K., a patient with severe allergic headaches, rhinitis and fatigue, whose case report has been published previously,[14] illustrates similarities in the blood response with intravenous doses of varying size. When improvement had been obtained as a result of the initial intravenous doses, small amounts administered intravenously or orally were sufficient to maintain clinical improvement.

of the previous intravenous dose; the interval between doses is similar. The clinical effectiveness of continued oral treatment persists for varying periods of time but may gradually diminish after the first month or six weeks. Under such circumstances it is often desirable to repeat one or two intravenous doses, following which oral therapy may again be effective.

As implied, some individuals respond more satisfactorily to oral therapy than others. The range in dosage is quite variable from person to person and considerable time is required to determine the most advantageous dosage level for a given case. Some patients tolerate oral therapy with a highly satisfactory degree of relief of allergic symptoms whereas even very small doses of Pyromen intravenously accentuates their clinical manifestations. As in the treatment of house dust sensitivity,[25] some allergic individuals require exceptionally small amounts of Pyromen in order to avoid the accentuation of symptoms and to produce an amelioration of the previously existing allergic manifestations. For instance, in two highly allergic individuals the oral administration of one drop of Pyromen solution containing 5 gamma per cubic centimeter (approximately one quarter of one gamma) has resulted in an

accentuation of previously existing allergic symptoms and led to the discontinuation of Pyromen therapy. This type of response, however, is uncommon.

It should also be emphasized that much larger doses of Pyromen may be given safely, at least to certain patients, than those recommended in this presentation. Relatively large intravenous doses may often be administered in the absence of severe reactions, particularly in the early phase of therapy, if successive treatments are given at such frequent intervals as once daily or on alternate days. This type of intravenous therapy has not been as effective in our hands as the schedules recommended. If the mechanism of Pyromen action is one of pituitary-adrenal stimulation, as will be subsequently discussed, lower dosage schedules would seem preferable. Once this sequence of oft-repeated doses is broken by several days without Pyromen therapy, it is wise to make a material reduction from the level of the last dose when treatment is resumed in order to avoid the production of a marked constitutional reaction.

In giving relatively large doses of Pyromen orally, one may encounter delayed reactions which are easily confused with apparent "wear-off" effects. When such successively large oral doses are given at frequent intervals, a clinical picture develops of increased general symptoms that is suggestive of the prodromal symptoms of influenza or the exhaustion phase of the alarm reaction as described by Selye.[37] However, it is freely admitted that the correctness of this interpretation is somewhat speculative at present. In fact, our present concepts of dosage are by no means final, and the currently recommended schedules may undergo considerable modification with further experience. It is of interest that we have become increasingly conservative in the direction of giving smaller doses at more infrequent intervals as our experience with this agent has increased. This conservatism has not resulted because of the fear of larger doses but is due to the appreciation of superior results obtained from the administration of the smallest dose in an individual case which will bring about effective relief of symptoms with minimal side reactions, and usually in the complete absence of such constitutional symptoms. This dose is then repeated at an interval just sufficient to maintain continued clinical improvement. The actual dosage schedule employed in different individuals and at different times in the same individual is highly variable; it not only depends upon the amount of previous therapy in a particular case but also to some extent upon the allergic manifestations presented, the relative degree of specific sensitivity of the patient in respect to his allergens, and probably upon several other factors, which most likely include the current lability of the pituitary-adrenal system in respect to the ease with which it may be stimulated to greater secretory activity.

RESULTS OF TREATMENT WITH PYROMEN

As most allergic individuals with perennial symptoms are sensitive to both inhalants and foods and as Pyromen therapy seems to be less effective in controlling inhalant symptoms than those from food sensitivity, patients allergic to house dust, silk, and other epidermals obtain more satisfactory results if specific inhalant therapy is combined with Pyromen treatment. Inhalant sensitivities have been diagnosed according to Rinkel's serial dilution technique of intradermal testing,[30,31] and specific treatment has been based upon the administration of therapeutic doses in relation to the individual's measured end-point of skin test reaction.[25,32] The combined treatment of inhalant sensitivities and intravenous or oral Pyromen therapy constitutes a workable program and results in more effective management of the allergy patient with perennial symptoms than may be obtained as a result either of inhalant management or Pyromen therapy alone.

A number of patients with specifically undiagnosed allergic manifestations were originally started on Pyromen treatment in the dosage schedules previously outlined in an effort to determine the effectiveness of this type of nonspecific therapy. Although many obtained a considerable degree of symptomatic relief as a result of intravenous treatment or the combined intravenous and oral Pyromen therapy, the results were in general less satisfactory than might be obtained from allergic management alone and it was difficult to effect sustained improvement in spite of various attempts to regulate the dosage of Pyromen. The addition of specific allergic inhalant diagnosis and treatment sufficed to bring about satisfactory results in many, but the more difficult cases required a specific food diagnosis in addition. In the latter group it was found necessary to eliminate at least one or two of the major food allergens in order to bring about sustained satisfactory relief of symptoms, even though both inhalant therapy and Pyromen treatment were also continued.

It should be emphasized that those uncontrolled food sensitive individuals who obtained relief of their allergic manifestations early in the course of Pyromen therapy may commonly have a recurrence of at least some of their allergic symptoms after a month or two of this type of treatment, even though combined with specific inhalant therapy. When Pyromen therapy is partially effective in relieving the symptoms of food allergy or when the relative effectiveness of this agent begins to subside, the allergic individual is apt to develop mild and transient reactions following ingestion of his specific food allergens. This has been observed to occur even though the food in question is ingested under correct conditions of testing,[27] whereas under similar circumstances prior to treatment with Pyromen the same food produced clinical responses of greater severity and much longer duration.

The advantages of a specific allergic diagnosis, both in respect to

inhalants and foods, should be apparent from this discussion, for, in general, Pyromen therapy has been found most successful in patients in whom a partial or complete specific allergic diagnosis has been made. It is particularly advantageous where help is most needed, namely, as an aid in handling the problems of food allergy in those cases in which it is difficult or impossible to avoid all incriminated foods. In certain adults and quite commonly in children Pyromen therapy at times relieves the symptoms of food allergy and allows the individual to return to a general diet, but this degree of improvement cannot be expected in all instances. In the majority of cases of food sensitivity treated with Pyromen it may be necessary to avoid one or two of the most highly allergenic foods while continuing the use of other dietary offenders on a rotating, diversified schedule.[29]. The actual problem in a given case should be appraised on the basis of the degree of sensitivity existing to various foods and the breadth of sensitivity in respect to the number of foods involved by the sensitization process.[24] .

There seems to be little difference in the response of various perennial allergic syndromes to Pyromen treatment, with the exception that certain cases of bronchial asthma and atopic dermatitis frequently require somewhat larger doses for optimum effects and in general fail to respond as well as the allergic syndromes characterized by less extensive structural changes. In addition to the usual manifestations of rhinitis, asthma, eczema, urticaria, headache, and gastrointestinal allergy, additional perennial syndromes described under the designation of allergic toxemia[35,36] or the fatigue syndrome of allergic origin[15,23] respond most favorably to Pyromen therapy. This condition includes such symptoms as unexplained weakness, listlessness, fatigue, myalgia, nervousness, and mild depression or melancholia.

Numerous patients with one or more manifestations of the fatigue syndrome, which may or may not be associated with more orthodox allergic expressions, have shown a striking response from Pyromen therapy. Certain students, exhibiting chronic listlessness, irritability, and minor manifestations of depression as well as impairment in comprehension in reading, shortened attention span and chronic sleepiness have received particular benefit from treatment with this agent. This has been evidenced by an improved sense of well-being, clearness in thinking, greater ability to do original work, and ability to read more rapidly and with increased comprehension, all of which has reflected in their general behavior and school performance. Furthermore, this response can neither be induced nor maintained as a result of placebo therapy. Similar observations of this type have been made independently by Fitch.[5]

It should be noted that Pyromen has not as yet been employed in the treatment of seasonal hay fever.

UNDESIRABLE EFFECTS OF PYROMEN THERAPY

In occasional instances we have seen some evidence of an increased bleeding tendency in patients treated with Pyromen. This was first observed in a male patient with peptic ulcer of many years' duration who developed an acute hemorrhage the evening following his second intravenous dose of Pyromen. Further therapy was not attempted. Several female patients have shown some disturbance in their menstrual cycles in that metrorrhagia and occasionally amenorrhea may occur; this is most commonly observed only during the first period of menstrual flow after the onset of treatment. Other bleeding tendencies have not been noted.

Two patients complained of transient rectal tenesmus the evening following each intravenous dose of Pyromen. A few have noticed the onset of herpes simplex shortly after the institution of Pyromen treatment, but this did not recur even though therapy was continued. Two patients with auricular fibrillation developed a more marked irregularity for a few hours immediately following intravenous Pyromen. In general, however, complications have been few and relatively minor.

DISCUSSION

With the advent of the recently accumulated knowledge of the function of the pituitary-adrenal system, it is becoming increasingly apparent that the beneficial clinical effects known to follow vaccine therapy may be related to this endocrine function rather than being explained solely on the basis of the anamnestic response or other immunological interpretations in the formerly limited meanings of such terms.

Evidence supporting the concept that Pyromen stimulates the activity of the pituitary-adrenal system consists of, first, the demonstration of Windle and associates[42] that the administration to rabbits of small doses of this pyrogenic material produces an hypertrophy of the zona reticularis of the adrenal cortex suggesting acceleration of cortical secretory activity.

Another point supporting this idea is the fact that the administration of a similar pyrogenic material to patients with malignant hypertension is followed by a material increase in the urinary corticosteroid-like substances; this was reported by Corcoran and Page in 1948.[3]

A third point in the chain of evidence is the marked similarity in the hematologic response following the administration of adrenocorticotropic hormone (ACTH), Cortisone and Pyromen, although the variations in the peripheral blood following therapy with these agents is not identical. For instance, the eosinopenia occurring after Pyromen is less complete and more transient than that following the administration of ACTH or even Cortisone. However, Pyromen seems to produce a more profound lymphopenia than does either ACTH or Cortisone. In general, these cellular changes are similar to those described by Selye[37] in the alarm reaction. Of particular interest to the allergist is the fact that the same

pattern in the peripheral blood elements is also produced following the ingestion of an allergenic drug[16] or food[18] in a specifically sensitized allergic individual. In fact, the initial transient leukopenia of such reactions has long been empirically associated with the production of allergic symptoms following the experimental ingestion of food allergens.[18,28,33,39]

A fourth indication that Pyromen may act in a similar manner to ACTH and Cortisone is the pragmatic fact that these agents are beneficial in the treatment of allergic conditions.[1,26,34] Comparative clinical studies in a small series of allergy patients treated serially with ACTH,[13] Cortisone,[21] Pyromen and Concentrated Adrenal Cortex Extract (ACE)[19] indicate that in the dosage schedules employed ACTH is the most effective, followed by Cortisone and Pyromen, with ACE a poor fourth.

Another point suggesting that Pyromen administration is associated with cortical stimulation and that the beneficial clinical effects of Pyromen therapy accrue therefrom is the marked difference in the clinical response from initial and subsequent therapeutic doses. Whereas the initial intravenous injection may bring about an improvement of allergic symptoms for only a few hours, once this mechanism has been adequately stimulated, subsequent therapeutic doses are much more effective.

It should also be emphasized that in the average allergic individual specific inhalant and food management is still the treatment of choice, for in many cases this is a simple, safe, and workable program. This statement is made in spite of the beneficial results of Pyromen and other endocrine therapy and in spite of the fact that thus far we have seen relatively few complications or contraindications from the therapeutic use of Pyromen. In our experience the most satisfactory results in inhalant allergy have been obtained by determining the current degree of specific sensitivity in accordance with the technique of serial dilution testing, and treatment based upon the results obtained therefrom.[25,30,31,32] Specific food sensitivity is determined on the basis of provocative individual food tests with the most frequently ingested items of the diet.[27]

The long-term effects of therapy with Pyromen, ACTH, or other similarly acting agents cannot be stated at present. Several allergic individuals receiving continuous treatment for the past eight months are still responding satisfactorily and have not had any obvious ill effects.

SUMMARY

This preliminary report summarizes our clinical experience with Pyromen in the treatment of 150 allergic patients.

Pyromen, a highly refined bacterial product containing complex polysaccharides, evidently exerts its beneficial effect in the treatment of perennial allergic manifestations as a result of stimulating the pituitary-adrenal system. When compared with other agents known to act through this system, it is less effective than ACTH or Cortisone, but nevertheless is a promising agent in the therapy of chronic allergic conditions. It is

particularly helpful when combined with specific allergic diagnosis and therapy. Unlike ACTH and Cortisone, Pyromen is effective when administered orally.

Recommended individual doses of this pyrogenic material vary from 0.5 to 10.0 gamma (micrograms). Within this range of dosage the febrile response is usually lacking.

REFERENCES

1. Bordley, J. E.; Harvey, A. McG.; Howard, J. E., and Newman, E. V.: Preliminary report on the use of ACTH in the hypersensitive state. Proceedings of the First Clinical ACTH Conference, Philadelphia, Pa.: Blakiston, 1950.
2. Chambers, W. W.; Koenig, H.; Koenig, R., and Windle, W. F.: Site of action in the central nervous system of a bacterial pyrogen. Am. J. Physiol., 159: 209-216, 1949.
3. Corcoran, A. C., and Page, I. H.: Methods for the chemical determination of corticosteroids in urine and plasma. J. Lab. & Clin. Med., 33:1326, 1948.
4. Dougherty, T. F., and White, A.: Influence of hormones on lymphoid tissue structure and function. The role of the pituitary adrenotropic hormone in the regulation of the lymphocytes and other cellular elements of the blood. Endocrinology, 35:1, 1944.
5. Fitch, E.: Personal communication.
6. Hamburger, J.: Le fond dyspneique latent des asthmatigues. Semaine de hosp. de Paris, 24:2257, 1948.
7. Hills, A. G.; Forsham, P. H., and Finch, C. A.: Changes in the circulating leukocytes induced by the administration of pituitary adrenocorticotropic hormone (ACTH) in man. Blood, 3:755, 1948.
8. Kierland, R. R., and Kulwin, M. H.: Clinical evaluation of a new pyrogenic agent. Submitted and accepted for publication in Arch. Dermat.
9. Lonsen, W., and Liebert, E.: Studies on a new pyrogen fever treatment. Illinois M. J., 96:186-190, (Sept.) 1949.
10. Nesset, N. M.: Personal communication.
11. Page, I. H., and Taylor, R. D.: Pyrogens in the treatment of malignant hypertension. Modern Concepts Cardiovas. Dis., 18:51-52, (Oct.) 1949.
12. Page and Corcoran: Arterial Hypertension. 2nd ed., pp. 328-330. Chicago: Year Book Publishers, Inc., (Sept.) 1949.
13. Randolph, T. G., and Rollins, J. P.: Adrenocorticotropic hormone (ACTH); its effect in bronchial asthma and ragweed hay fever. Ann. Allergy, 8:148, 1950.
14. Randolph, T. G.: Allergic headache, an unusual case of milk sensitivity. J.A.M.A., 126:430, 1944.
15. Randolph, T. G.: Allergy as a causative factor of fatigue, irritability and behavior problems of children. J. Pediat., 31:560, 1947.
16. Randolph, T. G., and Rawling, F. F. A.: Blood studies in allergy. III. Cellular reactions in sulfonamide sensitivity. J. Allergy, 16:17, 1945.
17. Randolph, T. G.: Blood studies in allergy. IV. Variations in eosinophils following test feeding of foods. J. Allergy, 18:199, 1947.
18. Randolph, T. G., and Rawling, F. F. A.: Blood studies in allergy. V. Variations of total leukocytes following test feeding of foods; an appraisal of the individual food test. Ann. Allergy, 41:163, 1946.
19. Randolph, T. G., and Rollins, J. P.: Concentrated adrenal cortex extract; its effect in bronchial asthma and gastrointestinal allergy. Ann. Allergy, 8:169, 1950.
20. Randolph, T. G.: Differentiation and enumeration of eosinophils in the counting chamber with a glycol stain; a valuable technique in appraising ACTH dosage. J. Lab. & Clin. Med., 34:1696, 1949.
21. Randolph, T. G., and Rollins, J. P.: The effect of Cortisone on bronchial asthma. J. Allergy, 21:288, 1950.
22. Randolph, T. G., and Rollins, J. P.: Eosinophil observations in adrenocorticotropic hormone (ACTH) therapy. Proceedings of the First Clinical ACTH Conference. Philadelphia, Pa.: Blakiston, 1950.
23. Randolph, T. G.: Fatigue and weakness of allergic origin (allergic toxemia) to be differentiated from "nervous fatigue" or neurasthenia. Ann. Allergy, 3:418, 1946.
24. Randolph, T. G.: Food allergy. M. Clin. North America, (Jan.) 1948.

25. Randolph T. G.: House dust allergy. Arch. Otolaryngol., 52:40, 1950.
26. Randolph, T. G., and Rollins, J. P.: Relief of allergic diseases by ACTH therapy. Proceedings of the First Clinical ACTH Conference. Philadelphia, Pa.: Blakiston, 1950.
27. Rinkel, H. J.; Randolph, T. G., and Zeller, M.: Food Allergy. Springfield: Charles C. Thomas, 1950.
28. Rinkel, H. J.: Food allergy. II. The technique and clinical application of individual food tests. Ann. Allergy, 2:504, 1944.
29. Rinkel, H. J.: The function and clinical application of the rotary diversified diet. J. Pediat., 32:266, 1948.
30. Rinkel, H. J.: Inhalant allergy. I. The whealing response of the skin to serial dilution testing. Ann. Allergy, 7:625, 1949.
31. Rinkel, H. J.: Inhalant allergy. II. Factors modifying the whealing response of the skin. Ann. Allergy, 7:631, 1949.
32. Rinkel, H. J.: Inhalant allergy. III. The coseasonal application of serial dilution testing (titration). Ann. Allergy, 7:639, 1949.
33. Rinkel, H. J.: The leukopenic index in allergic diseases. J. Allergy, 7:356, 1936.
34. Rose, B.: Studies on the effect of ACTH on eosinophilia and bronchial asthma. Proceedings of the First Clinical ACTH Conference. Philadelphia, Pa.: Blakiston, 1950.
35. Rowe, A. H.: Allergic toxemia and migraine due to food allergy. California & West. Med., 33:785, 1930.
36. Rowe, A. H.: Clinical Allergy Due to Foods, Inhalants, Contactants, Fungi, Bacteria and other Causes, Management, Diagnosis and Treatment. Philadelphia: Lea & Febiger, 1937.
37. Selye, H.: Textbook of Endocrinology. 2nd ed. Montreal: Acta Endocrinologica Inc., 1949.
38. Taylor, R. D.: Recent advances in the field of hypertension. Bull. Kansas Acad. Med., (in press).
39. Vaughan, W. T.: Food allergens. III. The leukopenic index, preliminary report. J. Allergy, 5:601, 1934.
40. Wells, J. A., and Rall, D. P.: Influence of adrenergic blocking drug (N-ethyl-N-(2-bromoethyl)-1-naphthylenemethylamine-HBr) on pyrogenic reaction. Proc. Soc. Exper. Biol. & Med., 70:169-171, 1949.
41. Wells, J. A., and Rall, L. P.: Mechanism of pyrogen induced fever. Proc. Soc. Exper. Biol. & Med., 68:421-424, 1948.
42. Windle, W. F.; Chambers, W. W.; Ricker, W. A.; Ginger, L. G., and Koenig, H.: Reaction of tissues to administration of pyrogenic preparation from a pseudomonas species. Am. J. M. Sc., 219:422-426, (Apr.) 1950.

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TISSUE CULTURE OF BLOOD LEUKOCYTES

(Continued from Page 625)

SUMMARY

What previously had been demonstrated in animals has now been shown to be true in man; namely, that the leukocytes of sensitized individuals are killed *in vitro* by the products of bacteria. The clinical applications of this fact have also been described. It was shown that when patients sensitive to one or several strains of bacteria are desensitized to these strains, their symptoms are usually allayed and their subsequent tests for sensitivity are negative. The effectiveness of the treatment of sensitive individuals was found to be dependent upon the specificity of the desensitization.

REFERENCES

1. Aronson, J. D.: J. Exper. Med., 54:387, 1931.
2. Heilman, D. H.; Feldman, W. H., and Mann, F. C.: Am. Rev. Tuberc., 52:65, 1945.
3. Moen, J. K.; J. Exper. Med., 64:355, 1936.
4. Rich, A. R., and Lewis, M. R.: Proc. Soc. Exper. Biol. & Med., 25:596, 1928.

METEOROLOGIC FACTORS IN THE DISTRIBUTION OF POLLENS AND MOLDS

A Review and Geographic Influence

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EVERY allergist is familiar with the almost universal complaint, "My asthma is always worse in damp weather," although most patients will admit that they have had relief from the use of steam kettles. This paradox indicates that the patients recognize a certain atmospheric condition which is associated with increased disability and mistakenly blame the water in the air for their trouble.

In the past three years we have been making airplane studies of the upper atmosphere which throw much light on the relationship of the weather to certain allergic disorders. A preliminary study[3] revealed that pollen grains and mold spores usually reached their highest concentrations in the cumulus clouds. The most interesting observation involved a day-and-night survey which showed that the maximum concentration of pollen occurred at varying altitudes during the day and night. A typical record of variations showed that the maximum concentration of particles climbed to about 6,000 feet from early morning until about midnight, when the level gradually fell to close to the ground at dawn. These undulations of pollens during the day and night were closely related to other observations. In general the level of maximum concentration was clearly visible either as a layer of haze, or clouds, or, in the early morning as a ground fog. It was also noticed that the air was most turbulent in the clouds, and that the haze or cloud levels marked the dividing layer between the bumpy lower air and the smooth upper air. No turbulence was experienced in or above the pollen- and mold-containing ground fog. Hay-fever victims were particularly miserable while the ground fog lasted and undoubtedly blamed the dampness for their trouble. Also, those who kept their windows closed at this time fared better than those who insisted on having "fresh air."

METEOROLOGIC OBSERVATIONS

Later observations[4] furnished the clue to the physical factors which are responsible for the vertical pollen and mold migrations. When air temperature observations[4] were included in the pollen and mold surveys, it became evident that the temperature of the air at various altitudes was responsible for the concentrations of particles at various levels. When the air was warm below and cold above, convection currents carried the pollen grains and spores to great heights, thus decreasing the concentration of allergenic particles near the ground. On the other hand, when the air failed to cool with increasing altitude (negative lapse rate), the upward currents

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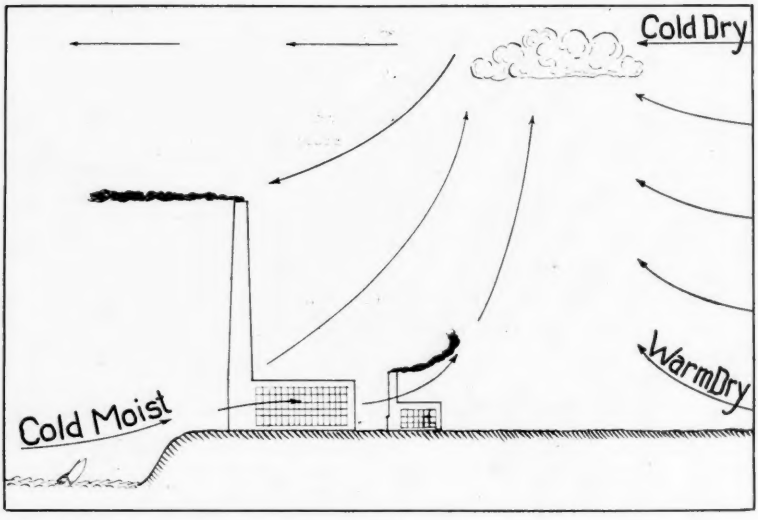

Fig. 1

TABLE I. WEATHER DATA, SEPTEMBER 5, 1948

	Madison					Milwaukee				
Time	Ceiling	Visibility	Temp.	Dew Point	Wind	Ceiling	Visibility	Temp.	Dew Point	Wind
1245	Scattered clouds 5,000 ft.	12	89°	58	ESE 15	Clear	10	80°	66	ESE 13
1315	Scattered 5,000 ft.	12	89°	58	ESE 15	Clear	10	80°	66	SSE 13
1415	High thin overcast Lower scattered 6,000 ft.	10	86°	50	ESE 10	High thin overcast	10	81°	66	SE 13
1545	Scattered 6,000 ft.	8	Missing	Missing	SSE 16	High thin	8	82°	64	SE 10

ceased and the particles remained concentrated nearer the ground. The worst condition was obtained when in the early morning the ground had lost much heat by radiation while the upper air remained warm (temperature inversion). The warm air, then, overlying the cold layer prevented upward currents. The ground fog results from the cooling of the air near the ground below the dew point.

GEOGRAPHIC FACTORS IN THE DISTRIBUTION OF POLLENS AND MOLDS

Durham[1] has made repeated surveys regarding the geographic distribution of pollens and mold spores. We are particularly indebted to him for his well-known pollen map of the United States. His observation that the west shore of Lake Michigan enjoyed lower pollen counts than regions farther inland, particularly when the wind was from the northeast, has been adequately confirmed. Even with a west wind, the air near the

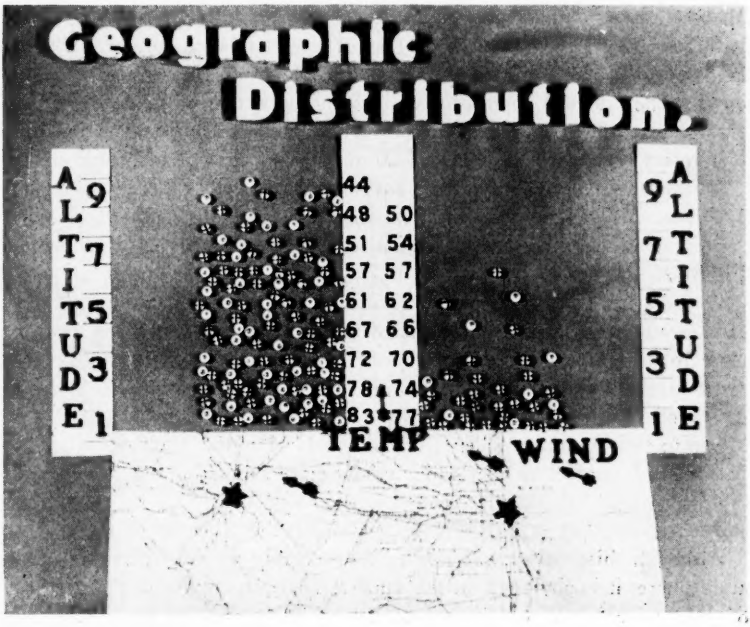

Fig. 2. The numbers at the sides represent the altitude in thousands of feet. The numbers near the center represent degrees of temperature on the Fahrenheit scale. The alternaria spores are shown as dots and the ragweed pollen grains as crosses. The star on the left side of the map represents Madison and the one on the right, Milwaukee.

TABLE II. VERTICAL SURVEYS, SEPTEMBER 5, 1948

Madison							Milwaukee						
Time	Altitude ft. above sea level	Temp. F.	Smuts	Alt.	Rag.	Remarks	Time	Altitude ft. above sea level	Temp. F.	Smuts	Alt.	Rag.	Remarks
1322	9500	44°	5	30	5	Between clouds							
1330	8500	48°	85	77	105	Between clouds	1530	8500	50°	0	3	3	Clear
1340	7500	51°	165	50	105	Between clouds	1541	7500	54°	0	0	5	Clear
1348	6500	57°	205	10	240	Below clouds	1549	6500	57°	0	6	5	Hazy
1355	5500	61°	220	150	163	Hazy	1555	5500	62°	5	10	10	Hazy
1402	4500	67°	185	105	190	Hazy	1602	4500	66°	10	20	25	Hazy
1409	3500	72°	105	130	150	Hazy	1608	3500	70°	20	20	45	Hazy
1418	2500	78°	165	205	260	Hazy	1618	2500	74°	35	50	135	Hazy
1425	1500	83°	200	160	205	Hazy	1625	1500	77°	175	65	350	Hazy

ground may be moving from the lake to the land, since the heavy colder air from the lake surface displaces the rising lighter hotter air over the ground. The visible evidence of this condition appears when the smoke from low chimneys moves westward while at the same time the smoke from tall chimneys is moving toward the lake (Fig. 1). Another interesting observation is that on a typical summer day when the winds aloft are westerly, the east wind on the surface is noticed for several miles inland. About 10 to 30 miles inland a stationary, narrow cloud gradually forms beginning

about 10:00 a.m. and building up till the tops are at times 5,000 feet high with bases at an average of 3,000 feet. These clouds extend parallel to the lake shore, i.e., running north and south. They disappear at about sundown. The practical application of this finding is that most hay-fever sufferers complain of increased discomfort when they are living in the summer resort region which is located 20 to 35 miles west of Milwaukee.

With easterly winds, vertical surveys were made at Milwaukee and Madison. Milwaukee is on the west shore of Lake Michigan while Madison is about 80 miles west. The information of Table II is shown in Figure 2.

An analysis of these data shows, first of all, cooler and more humid air at Milwaukee. The Milwaukee pollen grains and mold spores are few and close to the ground while those above Madison are plentiful and rise to great heights. The reason for this difference is that in Milwaukee the almost pollen free wind which blows over Lake Michigan has too short a sweep to pick up much pollen from the land, while the Madison pollen has been picked up after an overland wind sweep of at least 80 miles.

PRACTICAL APPLICATIONS

Although this survey was limited to the study of solid particles in the atmosphere, it is obvious that the same mechanism applies to the dispersal of gases. During World War I poison gases were found to be most efficient when temperature inversions occurred (warm air above—colder below). Even in times of peace, industries are pouring tons of equally poisonous waste products into the atmosphere with the hope that the wind and air temperatures are favorable for sufficient dilution of the gases to prevent poisoning. However unfavorable weather conditions, such as the inversion which lasted five days in Donora, Pennsylvania, in October, 1948, caused twenty deaths and illness of 5,910 persons—43 per cent of the population.[2] Those who died were chiefly older persons or those previously suffering from respiratory ailments or cardiovascular diseases. The Donora community also has a high incidence of bronchial asthma.

Knowing under what conditions of the weather particulate matter and gases remain close to the ground in high concentrations, the expression, "My asthma is due to dampness," takes on a new significance.

SUMMARY

Airplane studies indicate that a high lapse rate is responsible for the vertical dissemination of pollen and mold spores, and that a negative lapse rate and particularly a temperature inversion is responsible for maintaining a high concentration of allergenic particles near the ground.

The influence of Lake Michigan on pollen and mold dispersal is analyzed.

The analogy between illness caused by particulate allergenic material and that caused by industrial gases is discussed. Since the most obvious

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SHORTENING THE TREATMENT OF HAY FEVER

The Combined Antigen-Antihistaminic Technique in Pollen Therapy Study III

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THE advent of antihistaminic drugs has given a new impetus to the study of allergic diseases. At first, these drugs were employed primarily for relief of symptoms. More recently, a few investigators have suggested their concomitant administration with antigen extracts. Arbesman,[1] Fuchs,[2] and Green[3] observed that sensitive patients could tolerate larger doses of antigen when oral antihistaminic medication was given prior to the injection of the specific antigen. In a group of forty-five pollen-sensitive patients, Maietta[4] combined progressively increasing massive doses of pollen antigen with a twenty-four-hour simultaneous administration of suitable antihistaminic drugs orally with each injection.

The purpose of this paper is to present a new technique in pollen therapy. The method significantly decreased the number of injections; enabled sixty-five ragweed-sensitive patients to tolerate much larger individual doses than are customarily recommended, conferring upon them a very high degree of protection during the specific season; and produced uniformly satisfactory results.

TECHNIQUE

The sixty-five ragweed-sensitive patients were composed of two groups, a preseasonal and a perennial. Thirty patients, presenting themselves for initial treatment prior to the 1949 ragweed season, constituted the preseasonal group. Twenty of these who weighed more than one hundred pounds, received eight preseasonal, build-up injections of pollen antigen in 250, 500, 1,250, 3,000, 6,000, 10,000, 15,000, and 20,000 PU doses, a preseasonal total of 56,000 PU. Ten patients weighing less than one hundred pounds received the same number of injections but with a 50 per cent diminution in the individual doses. Preseasonal injections were given monthly, biweekly, weekly, or semiweekly. The pollen dosage schedule was so arranged that the eighth or last injection was given just before the season. Thirty-five patients, having received preseasonal therapy prior to the 1948 season, were in the perennial group and were given "maintenance or booster" injections of top pollen doses at bimonthly intervals, six throughout the year. Twenty-two of these had a top pollen dose of 20,000 PU and received 120,000 PU total; while thirteen had a top dose of 10,000 PU and were given 60,000 PU throughout the year. For

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both groups, the Coca-Noon pollen unit, containing 0.00001 mg of total nitrogen, was employed.

A dose of 50 mg of Thephorin was given orally twenty minutes prior to each injection. The injection was prepared by first withdrawing the desired pollen antigen dose followed by 25 mg (1 cc) of aqueous Thephorin,* a new parenteral antihistaminic agent, into the same syringe; inverting several times to mix both solutions; and administering subcutaneously into the arm three or four inches above the elbow. One hour later, a dose of 50 mg of Thephorin was given orally. No other medication was given preseasonally.

In order to expedite the calculations involved and to insure an accurate dosage in the withdrawal of both solutions into the same syringe, an allergy syringe† with a new dual 2 cc calibration was employed. On the right side of the barrel at the distal end, the first cc was graduated in tenths; on the other, both cc in quarters. The dose of pollen antigen, in any dilution, being withdrawn first, was easily measured in tenths; while the required amount of the aqueous antihistaminic preparation was added by utilizing the quarter cc calibration.

RATIONALE

Massive doses or inordinate increments of pollen antigen are likely to produce a constitutional reaction in a specifically sensitive patient. In our study, despite the administration of excessively large amounts of pollen extract, the patients were protected against a severe systemic manifestation by the employment of the combined antigen-antihistaminic technique. It appears that the antihistaminic Thephorin "neutralizes or inactivates" some "general-reaction-producing-substance," probably closely allied to histamine or H-substance, released locally at the site of the injection by the deliberate overdose of pollen antigen. The primary perimeter of inactivation is local, at the site of the injection, where the parenteral antihistaminic, deposited well in advance of the release of the "general-reaction-producing-substance," inactivates the histamine-like substance being released from the tissues. The secondary perimeter of inactivation is in the blood stream, possibly in the immediate vicinity of shock organ cells, where the oral antihistamine, absorbed from the gastric mucosa, is circulating and where any excess of the histamine-like substance, passing into the blood stream from the local reaction, is neutralized.

RESULTS

In the group of sixty-five ragweed-sensitive patients receiving the combined antigen-antihistaminic technique, there were twenty-five males and forty females. Fifty-one weighed more than one hundred pounds, and fourteen weighed less than one hundred pounds. Their ages ranged from

*Supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.
†Supplied by Becton, Dickinson & Co., Rutherford, N. J.

seven to fifty-six years. Throughout the 1949 ragweed season, the patients received no medication; remained in their usual environment; pursued their normal, daily routine; and did not utilize air conditioning or air filtering units. Each patient kept a clinical diary during the season and tabulated his own results daily. These were graded excellent (completely symptom-free), good (mild, fleeting symptoms during the peak of the season only), and fair (mild symptoms appearing intermittently throughout the season).

Clinical sensitivity to ragweed was established by the history and scratch skin tests with an extract of a 1-50 dilution. The latter were interpreted and correlated in the light of the history. By positive skin tests, twenty-seven patients (42 per cent) also exhibited associated sensitivities to trees, grasses, molds, or house dust. These, however, were unsubstantiated by the clinical history and, for the present at least, were deemed irrelevant.

Side Reactions.—Despite the inordinate dose of Thephorin administered within a relatively short time with each pollen injection, only nineteen patients (29 per cent) complained of side reactions. Insomnia was the most frequent manifestation. Drowsiness and lassitude occasionally occurred also. Side reactions were inconsequential, lasted from one half to two hours and never warranted discontinuance of the technique. Not infrequently, patients who complained of side reactions subsequently tolerated satisfactorily the large dose of antihistaminic medication.

Local Reaction.—Locally, slight itching, burning, or stinging generally accompanied an injection. These symptoms were transient and disappeared within a few minutes. The appearance of the local reaction was delayed from two to four hours in forty-three patients (66 per cent); while in twenty-two (34 per cent) it was evident in fifteen minutes to one hour. Usually the wheal was slight, but the erythematous flare was pronounced. The latter, however, was not always entirely due to the local action of the pollen extract; the slightly irritating effect of the aqueous Thephorin contributed to it also. The local reaction varied from 2.5 to 20 cm in size and lasted from a few hours to as long as thirty-six hours. Associated local tissue edema was proportionate to the size of the reaction.

Post-hyposensitization Skin Tests.—All the patients were retested routinely by the scratch method with a 1-50 ragweed extract within a few days after their last injection and just prior to the ragweed season. The size of the post-hyposensitization skin test was decreased in fifty-three patients about 50 per cent and in four about 25 per cent, while in eight no appreciable difference was noted.

Constitutional Reactions.—In a few patients, previously injected sites flared following subsequent administrations of ragweed antigen. This phenomenon was not classified as a constitutional reaction. Only three patients (4.6 per cent) developed mild, delayed, generalized symptoms consisting of sneezing, pruritus, angioneurotic edema, urticaria, and/or asthma. These symptoms appeared from one to several hours after the injection, lasted from a few minutes to four hours, and were readily controlled with additional oral doses of Thephorin.

In the preseasonal group, massive doses of pollen antigen were administered in rapid progression. Heretofore, these inordinately large amounts were considered inadvisable because of the hazard of constitutional reactions. In this group, two patients developed systemic manifestations. In one, the reaction occurred with the 1,250 PU dose (third injection) and, in the other, with the 3,000 PU dose (fourth injection). In both patients, the remainder of the intensive pollen dosage schedule was decreased 50 per cent. Despite this reduction, these two exquisitely sensitive patients still received high individual pollen doses and a total dosage far in excess of the amount they could have tolerated without the antihistaminic effect of Thephorin.

In the perennial group, (1) top pollen doses were administered instead of the substantially reduced amount of antigen as is customarily done in perennial pollen therapy; (2) the interval between injections was lengthened from the usual three or four to eight to ten weeks; and (3) the amount of antigen, given at a time when the blocking antibody titer was failing, constituted a deliberate overdose from which a systemic reaction ordinarily could develop. In this group, one patient exhibited mild systemic symptoms whenever the top pollen dose of 10,000 PU was administered.

Clinical.—The preseasonal treatment of hay fever for sixty-five ragweed-sensitive patients was shortened considerably and rendered more effective with the combined antigen-antihistaminic technique. Fifty-nine patients (90.8 per cent) had an excellent result and remained completely symptom-free throughout the season; five (7.7 per cent) had a good result and exhibited mild, fleeting symptoms at the peak of the season; and one (1.5 per cent) had a fair result with mild symptoms occurring sporadically during the season.

SUMMARY AND CONCLUSIONS

A new technique in pollen therapy, combining the simultaneous administration of large doses of pollen antigen and an antihistaminic substance, has been presented. The treatment of hay fever has been shortened significantly and rendered more uniformly effective by giving fewer but

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FATIGUE

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FATIGUE merits more medical attention than it receives. Careful surveys of patients are often neglected because, in so many instances, no organic disease can be found. The medical histories of these patients, when carefully analyzed, show that exhaustion to one individual may actually mean constant and severe air hunger, and to the next may only express a willful non-desire to live at the same tempo as his energetically inclined associates.

The material for this paper has been gathered only from those cases in which fatigue is the sole complaint and not an incidental complaint. Three per cent of new patients seen by me over a period of one year have fallen into this category.

The common medical impression is that the great majority of these cases are of psychosomatic origin. Unsolved personality problems; fear states involving physical, mental, or financial security; or an absolutely unreasonable number of hours spent in sustained mental or physical exertion, appear on first contact to offer the most reasonable explanation. I believe, however, with due respect to those dealing in psychological and psychiatric disturbances, that few cases of chronic marked fatigue are ever completely solved by only psychiatric care. The individual today who has no frustrations, no fears, no worries, no religious, domestic, political or employer conflicts, and who has complete harmony with his environment is, indeed, a rare person. Therefore, I feel that all of us have psychoneurotic and psychasthenic tendencies, but I am hoping to find out why Jones, with the same physical status and facing the same problems as Smith, will collapse and seek medical attention while Smith carries on.

This paper was not written with a preconceived idea of presenting it at an Allergy conference. However, I must admit that a certain stimulation came from the following observations. Before anti-histaminic drugs became available, I noticed that hay-fever victims, in addition to their localized rhinitis, complained frequently of utter exhaustion, even though nasal symptoms were well controlled with hyposensitization. This same phenomenon appeared when serum or pollen dosage overstepped the reaction equilibrium. More recently, an interest in food allergy has convinced me still further that the person with an allergic diathesis complains far more frequently of fatigue than do others. Finally, the presence of seasonal variations in cerebral accidents, cardiovascular accidents, musculo-skeletal complaints and psychological disturbances, makes one still more curious about allergic etiology.

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The first fifty consecutive cases with the sole complaint of fatigue are presented in the following charts:

TABLE I. CHRONIC DISEASE ADEQUATE FOR COMPLAINTS

Chronic amebic dysentery	2
Cancer of colon	2
Pelvic inflammatory disease	2
Peptic ulcer with obstruction	1
Chronic cholecystitis	1
Rheumatoid arthritis	1
Polycystic kidneys	1
Coronary sclerosis (failing heart)	1
Hypothyroidism	2
Active pulmonary tuberculosis	2
Total	15

TABLE II.
ANALYSIS OF GROUP WITH ORGANIC DISEASE INADEQUATE FOR COMPLAINTS

Anatomical diagnosis		Allergic type with identifiable allergens	Result
Arterial hypertension with early renal failure	2	2	Dietary exclusion alone—1—Well* 1—unchanged*
Early Parkinson's disease	2	1	Dietary exclusion—1—unchanged Intravenous histamine—1—improved
Asthenia and chronic upper respiratory infection	3	3	Hyposensitization—2—improved Inhalant avoidance—1—well
Menopause	4	2	Dietary exclusion—1—well Dietary exclusion and estrogens—1—improved Estrogen therapy—1—unchanged 1—improved
Compensated rheumatic heart disease—previously medicated to compensation	2	1	Inhalant hyposensitization—1—well 1—unchanged
Pelvic inflammatory disease	2	1	Dietary exclusion—1—well 1—unchanged till surgery
Total	15		

*"Well" or "improved" refers to "fatigue" only.
Cases well or improved of fatigue by allergic management—48 per cent.

TABLE III. ANALYSIS OF GROUP WITH NO ORGANIC DISEASE FOUND

Functional diagnosis		Allergic type with identifiable allergens	Result
Simple physical exhaustion—Overwork	3	1	Inhalant avoidance—1—well* 2—unchanged*
Anxiety neurosis and personality disorders	13	9	Dietary exclusion—4—well 1—improved Inhalant avoidance—2—improved Unchanged with allergy control—2 Psychiatric referral—2—improved 2—unchanged
Migraine—tension headaches	4	3	Dietary exclusion—2—well Inhalant hyposensitization—1—improved Psychotherapy—1—improved
Total	20		

*"Well" or "improved" refers to "fatigue" only.
Cases well or improved by allergic management—60 per cent.

The number in whom we were unable to establish anatomical or pathological physiological diagnosis is large. I believe that most physicians will agree that this is always true. By the term "allergic type" as used in the tables, I wish to make it clear that I mean those people who gave either a personal history of an allergic reaction or a family history of allergy.

The results indicated are too good. It raises the question of psychic reassurance or the thought that the patient may be carried along by the physician's enthusiasm.

Scientific reasoning for results obtained in this ill-defined syndrome is difficult. I believe one observation is important. People of an allergic type nearly always show vasomotor instability. They blush readily; they show—under stress—erythematous mottling of the neck and upper chest; frequently they have headaches, syncopal-like reactions to powerful psychic stimuli, vertigo, effort syndrome, labile blood pressure, transient paraesthesias and urticaria, and poorly sustained endurance. It is possible, then, that continued insult to the autonomic nervous system by allergens is of sufficient impact to produce fatigue in the same fashion that emotional trauma may produce so-called nervous exhaustion.

Psychologists may well point out that any medical explanation for fatigue is powerful reassurance to the patient, just as is psychotherapy. Yet most have had this treatment. They are, therefore, living in exactly the same environment with only one significant change, and that is the removal of certain inhalants, contacts or foods. If the latter is in itself sufficient psychotherapy, I have wasted your time and mine. For the present I am stubborn enough to hold to my original contention.

DISCUSSION

HAL M. DAVISON, M.D., Atlanta, Ga.—Fatigue is one of the most common symptoms elicited by medical history. Any patient with or without any other complaint and with any type of disease may suffer slight to extreme fatigue. Since physical, mental, and emotional stress all consume energy, it must be assumed that fatigue may occur from causes originating from any kind of stress. Usually, there occurs with all diseases fatigue proportionate to the severity of symptoms or to the seriousness of the pathological processes present, but modified by the individual's resistance.

All patients with fatigue whom we have studied from the allergic standpoint have had one or more proven allergic diseases. In some of these patients there has occurred extreme fatigue out of proportion to other symptoms and for which no other cause but allergy could be demonstrated.

We have been unable to demonstrate that sensitivity to inhalants will be a prominent cause of fatigue, but we have been able to relieve some cases of fatigue by omitting foods from the diet to which the patient is sensitive and able to reproduce the symptom by feeding the patient with these same foods. Milk has been the most prominent offender. We believe that fatigue quite frequently results from sensitivity to foods and that it should be classified as one symptom occurring in cerebral allergy.

I am glad that Dr. Meyer has carried his investigation further and studied patients who have no other symptoms but fatigue.

STREPTOMYCIN BLOOD LEVELS IN RABBITS FOLLOWING ADMINISTRATION WITH AN ANTIHISTAMINE

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SENSITIVITY occurs in patients being treated with streptomycin, and the frequent development of sensitivity or contact dermatitis in nurses administering the drug to patients has been reported by a number of workers.[1,3,6] Local reaction to aerosol streptomycin has also been recorded.[7] Antihistaminic drugs have been found of value in controlling some of the skin eruptions and other allergic symptoms resulting from streptomycin therapy.

Simon[4] has shown the antihistamine Decapryn* (Doxylamine) Succinate (dimethylamonoethoxy-methylbenzyl-pyridine) to be of value in the treatment of penicillin reactions and in the prevention of such reactions. The combination of penicillin and Decapryn Succinate Minergic Solution was reported to result in fewer reactions, to be practically painless on injection and to evoke blood levels comparable to those produced by pencillin alone. In studies conducted on rabbits injected with penicillin and Decapryn we found that the antihistamine had no effect on blood levels.[2]

Simon has suggested that antihistamines may be of value in combination with other drugs capable of eliciting sensitivity, and it seemed desirable to evaluate the effect of Decapryn on streptomycin and dihydrostreptomycin blood levels in rabbits.

The dosage of antibiotic in our experiments was 50 mg per kg body weight, and all injections were made in the posterior left thigh muscle. Bleedings were by intracardial puncture, and the assay was a modification of that described by Stebbins and Robinson.[5] The average weight of the rabbits was approximately 2.7 kg.

The antihistaminic solutions employed contained 15 mg Decapryn Succinate per ml, 5 ml being added to 1 gm vials of antibiotic.

The results of blood level studies on streptomycin are shown in Table I. It can readily be seen that levels induced by the combination of antibiotic and antihistamine were as high as, or higher than, those induced by the control preparation.

Table II shows that results with the combination of dihydrostreptomycin and Decapryn are essentially the same as those obtained with the antibiotic in saline.

Differences between median averages at given time intervals are probably of no therapeutic significance, and it is evident from the overall comparisons that Decapryn has little or no effect on the blood levels induced

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by streptomycin and dihydrostreptomycin. The results would indicate that Decapryn, whether proposed for prevention of sensitivity to streptomycin, or for concurrent administration when both drugs are required, is not contraindicated by inactivation of the streptomycin.

TABLE I.
STREPTOMYCIN BLOOD LEVELS

	Hours–gamma per ml		
	½	3	6
Decapryn Diluent—Rabbit			
1	99	38	10
2	88	35	7
3	86	38	8
4	86	32	—*
5	92	39	11
6	135	78	26
7	79	29	—
8	82	33	13
Median	85	36	9
Saline			
9	85	32	7
10	71	36	6
11	76	57	24
12	100	34	12
13	66	32	8
14	68	28	10
15	74	32	10
16	86	32	7
Median	75	32	9

*Level below 7ug per ml, approximate limit of assay.

TABLE II.
DIHYDROSTREPTOMYCIN
BLOOD LEVELS

	Hours–gamma per ml		
	½	3	6
Decapryn Diluent—Rabbit			
1	110	40	16
2	88	23	—*
3	86	36	—
4	86	41	—
5	94	41	10
6	134	67	29
7	84	21	—
8	74	15	—
Median	87	38	—
Saline			
9	80	33	—
10	90	27	7
11	81	27	8
12	70	32	—
13	97	32	8
14	102	19	—
15	105	23	—
16	102	23	—
Median	93	27	—

*Level below 7ug per ml, approximate limit of assay.

CONCLUSION

Rabbit blood levels achieved with combinations of streptomycin or dihydrostreptomycin and the antihistamine Decapryn were essentially the same as those induced by saline solutions of the antibiotics.

REFERENCES

1. Levin, S. J., and Moss, S. S.: Contact dermatitis from streptomycin. Arch. Dermat & Syph., 59:663-664, 1949.
2. Murray, F. J.; Taylor, B., and Foter, M. J.: Blood levels induced by penicillin-antihistamine preparations. Ann. Allergy, 8:240-244, 1950.
3. Rauchwerger, S. M.; Erskine, F. A.; and Nalls, W. L.: Streptomycin sensitivity. Development of sensitivity in nursing personnel through contact during administration of drug to patients. J.A.M.A., 136:614-615, 1948.
4. Simon, S. W.: Hypo-allergic penicillin. Ann. Allergy, 8:194-201, 1950.
5. Stebbins, R. B., and Robinson, H. J.: A Method for Determination of Streptomycin in Body Fluids. Proc. Soc. Exper. Biol. & Med., 59:255-257, 1945.
6. Strauss, M. J., and Warring, F. C., Jr.: Contact dermatitis from streptomycin, preliminary report. J. Invest. Dermat., 9:3, 1947.
7. Wiener, J. J., and Lederman, F. W.: Local and systemic reactions to aerosol streptomycin; Case. M. Rec., 161:153-155, 1948.

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NUTRITIONAL THERAPY IN THE MANAGEMENT OF RESPIRATORY ANAPHYLAXIS OR ALLERGIES

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DISCUSSION OF DETOXICATION

As the preliminary feature of this presentation, we believe that a discussion of detoxication is of prime importance in the over-all contemplation of the broad study of anaphylaxis. The very word, anaphylaxis—from the Greek, meaning backward protection—suggests the deficiency of natural biologic forces, namely, immunogens, antibodies or detoxicants in the organism, essential to combat the invasion of sensitizing agents whether they be undigested proteins, by-products of bacterial growth or decomposition, or other toxic substances.

It has been brought out repeatedly in the current literature that detoxication is a fundamental mechanism to be considered in allergic response to antigenic agents. For example, we have sensitized a group of animals to horse serum. One-half of the subjects receive enzymatic protein digests and vitamins; the others do not. The nutritionally protected group survive with no evidence of tissue necrosis or the Rich anaphylactic lesions while the unfortified animals die with Rich lesions, hemorrhage, edema, thrombosis or collagen degeneration.

It has been hypothesized that if various toxic agents such as chloroform, snake venom, thyroxin or a lethal dose of diphtheria toxin can be oxidized, reduced and excreted as a non-toxic substance, the course of tissue degeneration (histotoxicosis) in disease should be manageable before material destruction or death takes place. This preventive biologic mechanism is accurately termed detoxication. Some outstanding examples of detoxication may be appropriately stated at this time. Pellagra occurs only in subjects suffering a state of protein depletion brought about by toxic destruction of tissue, and cured by nicotinic acid and enzymatic protein digests meeting the amino acid and strepogenin standards specified by Wooley and Peters,[9,13]

However, pellagra is not necessarily due to a nicotinic acid deficiency *per se*. It may be traced in certain instances to the blocking action of an analog such as 3-acetyl pyridine found in corn. This mechanism is typical of many metabolite deficiencies. The metabolite and its structural analog compete for position in the particular enzyme chain reaction which must proceed normally for metabolic needs. This phenomenon finds a parallel in many allergenic reactions; for example, antigenic agents block metabolites and cause eczema, but when an enzymatic protein digest is introduced in therapy, the detoxication properties of this substance prevent the disorder.

The work of Claussen offers still another parallel. This investigator showed that during infectious periods, the fat and water soluble vitamin reserves were severely depleted. More recently, it has been found that crude liver, folic acid and enzymatic protein digests re-establish assimilation. We are of the opinion that the normal individual in a state of health is equipped to combat most infections. This protective mechanism depends largely on the availability of adequate amino acids, strepogenins and vitamins through the diet and/or medication and the ability to utilize these factors by normal digestive processes. Psychosomatic elements must be ruled out when considering the latter, as fear, worry or tension may interfere with digestion, thus causing nutritional depletion.

It is felt that the development of natural resistance to foreign proteins is purely a problem of biological adaptation to environment. States of histotoxicosis or protein depletion, whether innate or acquired, interfere with the normal process of adaptation. An inflammatory adaptation takes its place and may only be corrected by eliminating the histotoxicosis through the re-establishment of normal amino acids, strepogenin and vitamin levels, and utilization of these agents. This is understandable in the consideration of infants with pancreatic deficiency who show marked deficiency in all the oil soluble vitamins, fail to grow and frequently go into hypocalcemic tetany because of vitamin D deficiency. These infants are anemic and are subject to colds and staphylococcal infections. We find that when treated with pancreatin and enzymatic protein digests these infants grow and gain weight rapidly. All this further emphasizes the importance of considering the action of toxins, both endogenous and exogenous in the study of disease and the necessity for regarding nutritional enzyme systems as detoxifying influences as well as basic material for new cellular replacement and growth.

ANAPHYLAXIS IN THE BROAD CONCEPT

Inability to utilize normally the basic nutritional factors constitutes a fundamental defect in those of so-called allergic constitution. In these patients, sensitizing antibodies are present in the organism instead of natural factors of resistance. It must be stated that a natural resistance to an infection or an antigenic invasion, implies a cellular state existing without injury in a toxic substrate.

The untreated patient in most instances shows a persistently negative nitrogen balance brought about by uncompensated toxic protein loss. These patients, in a state of suboptimal nutrition, demonstrate characteristic manifestations of allergic response to antigens, namely, Rich lesions, Schwartzmann reactions, hypermotility of smooth muscle, increased susceptibility to Gram-negative bacterial invasions with penicillinase resistance to treatment with penicillin. The latter may be attributed to the fact that in the state of suboptimal nutrition common to the allergic patient, peni-

cillinases are produced sufficient to inhibit concentrations up to 800 units per ml. Thus it becomes necessary to treat these patients successfully with other antibiotics such as Aureomycin for example.

All this has been explained in terms of toxic protein loss; in treating these patients, it is not sufficient to attempt bringing about an adaptation to a faulty biologic environment by elimination diets, desensitizing treatment schedules and symptomatic drugs such as aminophylline, theophylline, sodium glycinate, phenobarbital and belladonna. It is of supremely greater importance to institute a rich nutritional schedule using intravenous amino acids and plasma. In dealing with the constitutionally allergic patient, shock tissue is not confined to the bronchioles and the alveoli. The heart, liver, skin, gastrointestinal tract, in fact, any part of the entire organism may be involved. In the treatment of these patients, we proceed conventionally at first, providing symptomatic relief, as well as attempting to condition the patient to the abnormal biologic environment inherent to the allergic individual. Upon simultaneous administration of intravenous amino acids and oral enzymatic protein digests, we are able eventually to place the patient in a state of nitrogen balance, arresting and even reversing the toxic protein loss, provided we employ salines and plasma infusions according to the technique of Barclay Parsons along with symptomatic treatment (aminophylline gr 7½; phenobarbital gr 2½; epinephrine 0.3 cc).

Upon the achievement of this objective, the so-called allergic constitution becomes a somewhat less difficult problem. Sensitized tissue becomes more readily desensitized. Degeneration, due to anaphylaxis, is prevented by the better ensuing nutritional status of the patient.

We are able to point to patients originally diagnosed generally allergic and who with a persistent infection, when treated as described, emerge as different individuals. As their infections come under control, the allergies become less manifest and more readily manageable. Hyperergic skin tests become completely negative after the optimal nutritional state has been achieved. The patient may become freely exposed to pollens or ingest foods to which he was highly sensitized and which before nutritional treatment would have precipitated a marked anaphylactic reaction and even death.

It is interesting to note, too, that the allergic patient untreated nutritionally shows a marked lack of resistance to bacterial infections; these individuals display a high incidence of sinusitis, pneumonia (all types) and other states often ineffectively treated with antibiotics because of prevalent histotoxicosis.

But how about "non-allergic" patients brought into a state of malnutrition from conditions such as severe infections, diabetes mellitus, hepatitis, pregnancy, liver cirrhosis, burns, overwork, alcoholism, et cetera? These subjects, too, show many of the symptoms and stigmata char-

acteristic of the true allergic. They all suffer a severe toxic loss of protein frequently with increased susceptibility to infection, hypermotility of smooth muscle, hypersecretion, Rich lesions, Schwartzmann reaction, edema and asthma.

Until toxic loss of protein is checked with enzymatic digests* (both oral and parenteral) blood plasma injections and accompanying vitamin therapy, if necessary, an anaphylactic state persists with an increasing involvement of the entire organism as shock tissue. Nitrogen balance is the goal in these cases and not until accomplished is control established.

We have treated patients who have been referred for psychiatric management. A female in particular was relieved by aminophylline parenterally (7½ gr). With the removal of a tooth and subsequent treatment with penicillin and streptomycin, allergy to house dust disappeared. This was only transitory however; three years later, severe asthma returned soon after a fractured arm was sustained. The nutritional status was so poor that it took six months to effect union in the fracture. Many cases of "invalidism" begin with the inability to maintain nitrogen balance. Acquired allergies and mold infestations so prevalent in these conditions are due primarily to nutritional failure. Many of these patients show characteristic reactions to house dust and ragweed, but are free of symptoms until nutritional failure due to surgery, infection or fracture, intervenes.

According to M. B. Strauss,[12] pregnancy toxemias are due in great measure to diets low in protein. By establishing biologic balance, thus checking protein loss, we are able to prevent convulsions, cut down edema and reduce to normal, hypersecretion and hypermotility of the smooth muscle. Of special consideration in nutritional failure, incident to pregnancy, is the frequency of anemia. Blood dyscrasias of particular gravity are of the macrocytic type. We are able to find no incidence of obstetrical anemia when the daily intake of protein approaches a value of 75 gm daily. Often, it becomes impossible to provide adequate protein needs through dietary sources alone. Co-Tui has stated that pregnant women with pernicious vomiting were better able to tolerate oral protein hydrolysate than natural foods.

The pediatrician too, as attested by Hill,[5] Olmsted,[8] Hartman[3] and many others, finds that hydrolysate substitution and boosting in milk feedings re-establishes the integrity of the skin, and by aiding the development of natural resistance generally alleviates the allergic syndrome in infancy. Children in a state of toxic protein loss often show sensitivity to penicillin. The increase of protein intake to 5 gm/kg per day, with protein hydrolysates, has been preeminently successful in decreasing this sensitivity as well as alleviating, even curing the stubborn sinusitis, hay fever and other urticarial manifestations of sensitization.

*Protein Hydrolysate-MRT for oral use employed in our studies.

That the nutritional state of the infant is of profound importance in explanation of ability to combat infection, is shown by my patients, identical twin girls, living together, with marked difference in resistance to disease.

Their mother who gave positive skin tests to feathers, spring grasses, house dust and ragweed was cured of relapsing bronchitis. After treatment for a type 111 pneumococcus pneumonia with 100,000 unit doses of penicillin every three hours parenterally, combined with aerosol and aerosol suction, she lost both her clinical and skin tests to allergies.

Twin A ate well all foods, especially meat; refused all vitamin therapy and had no illnesses. Twin B received Vitamins A and E (Claussen) and Procholon to stimulate her appetite and for protection, in spite of which she contracted all diseases to which she was exposed. Both twins were nervous but with adequate diets their behavior reactions to medication became better than the average.

In the past three years, Twin B had many streptococcic and pneumococcic infections with hyperemesis, otitis media, sinusitis, tonsillitis, measles, mumps, scarlatina, rubella and pyelonephritis. During these illnesses of Twin B, Twin A took only 1 teaspoonful of sulfadiazine with sodium lactate each day, as a preventive measure, and showed no signs of infection.

When the above infections were cured in Twin B she was put on protein hydrolysate, panteric crystals and pancreatic capsules with bile acids, Folvite, and gamma globulin (2 cc a week). Vitamin therapy of all kinds was discontinued. She developed an appetite and intake as good as that of Twin A. For the past year there has been no illness. Her growth is now greater than Twin A.

In general, upper respiratory conditions, including rhinitis, bronchitis, sinusitis and the like, either of allergic etiology or not, all show toxic protein loss. Whether or not the active infection is due to the hypoproteinemia associated with allergy or to the toxic protein loss brought about by bacterial invasion or fracture, is not the main issue. In either instance, we must administer antibiotics such as aerosol or parenteral penicillin, streptomycin, sulfonamides, Aureomycin and Chloromycetin as well as persist in our efforts to achieve a state of optimal nutrition in our patients with intravenous amino acids and oral protein digests.

In treating respiratory disease, we must forever be conscious of this concept, often neglected in general practice. Certainly, penicillin and other chemotherapeutic agents are successful in the nutritionally depleted patient—but only up to a certain point. Get that patient in nitrogen equilbrium by checking histotoxicosis! Not only will the entire antibiotic value of the drug be realized, but the patient will be equipped to combat the frequent recurrences so often encountered in the chronic sinus and rhinitic patient. We have proven this over and over again in our own

practice. It is our observation that patients in a sound nutritional state do not develop sensitiveness to penicillin or become penicillin-fast because of penicillinases; furthermore he does not demonstrate the characteristic urticaria and/or angioneurotic edema associated with an allergic disturbance. It may be appropriately stated that chemotherapeutic agents introduced into the nutritionally adequate patient are free to act antibiotically and not antigenically.

Surgical patients, both preoperatively and postoperatively, are invariably in an anaphylactic state. Admitted to the hospital, they have often used up all reserves, showing suboptimal nitrogen levels which cannot be reestablished by even generous diets. Mulholland,[7] Stengel, Ravdin,[10] Co-Tui,[2] Davidson[11] and others have reported on the necessity of taking these facts into consideration in the medical management of the surgical patient and have recommended intravenous amino acids, oral hydrolysates and often therapeutic vitamin therapy as well, before and after surgery such as gastrectomy, cholecystectomy and herniotomy. They report shortened convalescence, improved tone, increased resistance to infection, disappearance of edema and quick promotion of gastric emptying time. Surgical shock or injury may account for the loss of 20 to 40 grams of nitrogen daily (1.5 to 3.0 pounds of tissue) due to toxic destruction of protein.

We have observed on the Surgical Metabolism Ward at Presbyterian Hospital, that by using shock therapy and oral hydrolysates* equivalent to 85 grams of protein daily, even the initial three days of toxic protein loss, which Peters has stated was inevitable, has been averted. Barclay Parsons believes that toxic protein loss as manifested by surgical shock may be entirely eliminated by these measures despite the ideas of Peters who has preached a doctrine of "let nature take its course."

Relative to the nutritional concept in practice, it is thus seen that there are two prevalent schools of thought. According to Peters, the nutritional status of the patient, brought into negative balance through surgery, infection or whatever cause, will right itself as a matter of incidence after a return to normal status. On the other hand, we of the opposite school have observed that this concept is fallacious. If something is not specifically done about the toxic protein loss, patients are never given a chance to recover. There is persistent retarding of the patient's ability to combat infection; sensitization is acquired instead of natural immunity with resulting disturbances ensuing, prominent of which is respiratory anaphylaxis. Toxic loss of protein sets in after an operation and after struggling to keep alive at a daily occupation for five years or more, cardiac, liver and/or kidney function often shows progressive failure.

We have found repeatedly that these patients do not respond to the

*Protein Hydrolysate-MRT

so-called adequate diet—the beefsteak of Peters so to speak; they cannot eat in the hospital two or three weeks postoperatively and continue to half-live in a state of negative nitrogen balance for years attended by chronic and persistent infections.

This picture is changed with today's accent placed on therapeutic nutritional measures as described to check toxic protein loss.

The application of complete nutrition to surgery is not simple; it involves the consideration of the following factors: optimal weight of patient, observed weight, plasma protein, plasma albumin, plasma volume, nitrogen intake and output.

The orthopedic surgeon, too, is becoming nutrition conscious. Howard[6] and his associates at Johns Hopkins, in his studies of nitrogen balance during fracture convalescence, found that the human with fracture suffered a markedly increased catabolic rate resulting in large losses of tissue even though the diet supplied theoretically ample protein. A fractured tibia ingesting 120 grams of dietary protein could not maintain nitrogen equilibrium; he lost about 200 grams of tissue nitrogen during the first thirty days after injury. We must remember that bone is laid down over a protein foundation, and that this stroma must be repaired before bone is actually regenerated. Hypoproteinemia thus interferes with fibroblastic repair and also tends to reduce serum calcium because half the serum calcium is bound to serum protein.

The nephritic and nephrotic patients present invariable signs including tissue depletion, hypoproteinemia, proteinuria, hypertension, hypermotility of smooth muscle and hypersecretion. With blood levels falling to 2.5 per cent for albumin and 5.5 per cent total protein, edema appears and progresses as values fall still further. We find that intravenous feedings and enzymatic yeast digests elevate protein values with great rapidity.

Medical literature describes at length heart abnormalities closely associated with nutritional failure and the converse. The so-called "Beriberi heart" is not a manifestation of mere thiamine deficiency, but of the entire B complex, amino acids, et cetera. Youmans[14] states that protein deficiency brings about dyspnea, lessened blood volume, and finally actual loss of heart muscle substance. Bradycardia at rest is observed in more severe cases and, with hypothermia, hypotension and low metabolic rate, usually goes along with a state of malnutrition.

Other clinical pictures faced by the cardiologist such as congestive heart failure, coronary insufficiency, acute coronary thrombosis, active carditis, or circulatory shock are closely allied with failure in intermediary metabolism. From this metabolic failure, anoxia causes retardation of tissue oxidations because of important co-enzyme destruction. Pyruvic acid metabolism becomes defective; the extent of pyruvemia is a measure of the degree of heart failure. Hermann states:[4]

"Feeding of high protein, acid or neutral ash, as well as sodium free diets are indicated in most patients with congestive heart failure and edema. Proteins of good biological character may be supplemented with protein hydrolysates, amino acids, yeast or choline."

Good nutrition is an important phase for the clinician to consider in attempting fortification and therapeutic support to compensate for the defects of intermediary metabolism in the cardiac patient.

Of the allergic patient in cardiac failure, we can say the heart is shock tissue with the anaphylactic symptoms described in terms of the foregoing and identical with them. Whether or not the cardiac involvement is an outgrowth of an allergic constitution or brought about by infection, renal failure, fatigue or any cause whatever, we find that these patients respond to therapeutic nutritional measures as described. True, we treat these patients symptomatically and palliatively with digitoxin, aminophylline, barbiturates, et cetera, but if we hope to arrest the degenerative process, yes, even reverse it in certain instances, the nutritional attack is the only measure of true curative significance.

We can discuss virtually every medical problem in the light of the foregoing—namely, that of anaphylactic shock brought about by toxic protein loss, liver cirrhosis, burns, peptic ulcer, diabetes, geriatrics, alcoholism, dermal dyscrasias, certain hearing and neuropsychiatric disorders.

The main attack in anaphylaxis is nutrition—dramatic therapeutic nutrition. Of most importance are intravenous hydrolysate feedings supplemented with enzymatic protein digests from yeast which contains the streptogenins stressed by Woolley to be of great significance. The development of quick protein levels at the beginning of treatment in severe anaphylaxis, by parenteral administraton of blood plasma, amino acids or hydrolysates, may be mandatory.

Peters of Yale takes considerable issue with us on my somewhat emphatic insistence on the use of hydrolysates as the preferred source of protein in these cases. Peters has stated that beefsteak or an equivalent dietary protein source is just as good, if not better; moreover, it is cheaper and considerably easier on the digestion and palate. Peters claims that only in the exceptional case is the employment of an amino acid injection or a protein digest necessary and therefore advisable.

We believe that Peters has failed to take into consideration the fact that in patients of allergic disposition, more often than not, whole protein is difficult if not impossible of digestive breakdown. This introduces the constant hazard of whole or partially digested protein entering the organism, augmenting the anaphylactic state or even precipitating further attacks.

And what about these patients with pancreatic, liver, and gastric dysfunction brought about through malnutrition, alcoholism, cirrhosis,

pregnancy, ulcer and a host of other conditions? These patients need protein, but in many instances cannot obtain their requirements from the dietary no matter how rich, due to reduced pancreatic function often present.

CONCLUSIONS

In conclusion, let us state that the anaphylactic state commonly associated with those of so-called allergic constitution cannot truly be differentiated from shock as observed, in the many phases of medical practice enumerated in this paper. They all are characterized by toxic loss of protein (histotoxicosis), hypermotility of smooth muscle, hypersecretion and the involvement of any organ of the body as shock tissue. And anaphylaxis in the broad sense can be managed in the true curative manner only by the use of true therapeutic nutritional measures, the more prominent of which are intravenous feedings of protein hydrolysates or amino acids supplemented by oral digests and vitamins if necessary.

We may also add that with the acquiring of positive nitrogen balance, there is virtually no digestive disturbance, sensitiveness to penicillin or other potential antigens. These factors are readily neutralized and eliminated by an actively functioning liver. The mechanism of detoxication by amino acids is so important during all phases of living that we may conclude that many of our important enzyme systems lose their important vitamin components during periods of negative nitrogen balance. We should also reaffirm that in the bringing about and maintenance of positive nitrogen balance, the most dramatic observations are at hand with intravenous therapy.

Sometimes, one or two intravenous feedings will accomplish more than it would seem possible from the relatively small amounts of protein-vitamin introduced into the circulation. After one such feeding, a patient, often with poor appetite, is able to maintain nitrogen balance by diet alone. Anorexia, in the surgical patient, for example, is often overcome in a matter of twenty-four hours. This very same anorexia after illness and surgery, customarily seen in the hospitalized patient, may persist for five to ten years with developing hepatitis and marked by negative nitrogen balance and a state of chronic infection characteristic of the malnourished. Again the answer here is nutrition as described, along with the program advocated, employing symptomatics and antibiotics as indicated.

Acknowledgment is made to Marvin R. Thompson, Inc. whose generous contributions of nutritional and vitamin materials have aided greatly in making this study possible.

REFERENCES

1. Claussen, S. W.: The absorption of vitamin A and its storage in tissues. Harvey Soc. of New York Lectures, 38:199, 1942-1943.

2. Co-Tui; Wright, A. M.; Mulholland, J. S.; Carabba, V.; Barcham, I., and Vinci, V. J.: Studies on surgical convalescence. Ann. Surg., 120:99, (July) 1944.
3. Hartman, A. F.; Meeker, C. S.; Perley, A. M., and McGinnis, H. G.: Studies of amino acid administration; utilization of enzymatic digest of casein. J. Pediat., 20:308, (March) 1942.
4. Hermann, G. R.: Blood plasma protein in patients with heart failure. Ann. Int. Med., 24:893, (May) 1946.
5. Hill, L. W.: Amino acids as a source of nitrogen for allergic infants. J.A.M.A,. 116:2135, (May 10) 1941.
6. Howard, J. E.; Parson, W. K.; Eisenberg, S., and Reidt, V.: Studies on fracture convalescence: influence of diet on post traumatic nitrogen deficit exhibited by fracture patients. Bull. Johns Hopkins Hosp., 75:209, (Oct.) 1944.
7. Mulholland, J. H.; Co-Tui; Wright, A. M.; Vinci, Y. G., and Shafiroff, B. G. P.: Protein metabolism and bed sores. Ann. Surg., 118:1015, (Dec.) 1943.
8. Olmsted, W. H.; Harford, C. G., and Hampton, S. F.: Use of synthetic diet for food allergy and typhoid. Arch. Int. Med., 73:341, (April) 1944.
9. Peters, J. P., Jr.: Problems of nitrogen metabolism. Federation Proc., 3:197, (Sept.) 1944.
10. Radvin, I. S.; Stengel, A., Jr., and Prushankin, M.: Control of hypoproteinemia in surgical patients. J.A.M.A., 114:107, (Jan. 13) 1940.
11. Stare, F. J., and Davidson, C. E.: Protein: its role in human nutrition. J.A.M.A., 127:895, (April 14) 1945.
12. Strauss, M. B.: Observations on the etiology of toxemias of pregnancy; etiologic relationship between water retention and arterial hypertension. Ann. J. M. Sc., 196:188, (Aug.) 1938.
13. Wooley, D. W.: Some correlations of growth promoting powers of proteins with their streptogenin content. J. Biol. & Chem., 162:383, (Feb.) 1946.
14. Youmans, J. B.: The clinical detection of protein deficiency. J.A.M.A., 128:439, (June 9) 1945.

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BRONCHIAL ASTHMA IN SMALL COMMUNITY HOSPITALS

(Continued from Page 621)

1. A thorough allergy survey to include history, family history, x-ray examination, and laboratory examinations for eosinophiles in the blood and in the nasal secretions.

2. Preventive treatment, skin tests, avoidance and elimination of offending allergens and education of patient and doctor in the widespread incidence of asthma.

3. Specific desensitization.

4. Judicious and proper use of drugs of choice in the acute attacks with a specific warning against the use of narcotics.

5. A well-equipped, air-conditioned, air-filtered asthma room in every hospital.

BIBLIOGRAPHY

Kenosha Hospital. Records of 1943-1947.
St. Catherine's Hospital: Records of 1943-1947.
Unger, Leon: Bronchial Asthma. Springfield, Illinois: Charles C Thomas, 1947.

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THE APPLICATION OF PSYCHODYNAMIC CONCEPTS IN AN ALLERGY PRACTICE

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IT is now generally agreed that the conditions we are called upon to treat cannot all be explained in their entirety on an antigen, antibody basis, nor can they all be treated successfully immunologically or pharmacologically alone. It is also generally accepted that emotions, such as anger, hostility, envy, or guilt, can produce specific physiological changes which either may set in motion allergic symptoms or protract or prevent recovery from them. I believe that in the majority of patients we see it is not a question of *either* allergic or psychosomatic but *both* allergic and psychosomatic, since both psychological and allergic factors can play a part in the cause and influence the course of the diseases we are treating.

The terms psychosomatic and psychodynamic are new, but what they describe is not. It has always been known that we blush with embarrassment and get pale with fear, that feelings are accompanied by certain physiological changes, neurovascular in nature, which can be observed objectively. Primitive man had to fight in order to live, and when outnumbered or confronted by greater strength, had to, and did, run. This "fight or flight" mechanism is still with us, in spite of the fact that we do not always fight or run when confronted with obstacles. In the face of danger to the organism, the vegetative functions prepare for "fight or flight." In persons suffering from neurotic conflicts, normal expression of certain emotions is blocked because of repression and inhibition, resulting in chronic emotional tension with ensuing disturbances of the vegetative nervous system.

In the last few years, I have tried to evaluate and treat both the allergic and tension components in my patients; and this paper is an attempt to discuss the new orientation I had to acquire before I could do so.

Regardless of the psychopathologic school to which one adheres, the fact remains that each psychosomatic reaction encountered is the end result of an individual's attempt to meet some life situation.

The first adjustment I had to make was in the taking of the history, because many facts about the patient's past and present life situation, which previously did not seem important to me, now assumed great importance, since they gave me an idea of past patterns of behavior. I also had to learn that what the obtained data meant to the patient or how he felt about them was the most important question. What emotions did the patient show when he talked about his parents, husband or wife, sisters, brothers, or employer?

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The second thing I had to realize was the fact that to be sick means to be dependent on others and that a patient's relationship to the doctor is not like that of one adult to another, but more like that of a child to a good parent. Therefore, just being the kind of doctor who understands those dependency feelings will help the patient. That the physician's personality is an important therapeutic tool with which he works has long been known. However, since we are dealing with the patient's feelings, the first and most important requirement for the doctor is to be objective about his own feelings. If the doctor himself is a rigid person and is unable to be objective about his own emotions, he will not be able to help these patients, because he will be hypersensitive or blind to those things in the patient which he has repressed within himself. This may explain why one physician can help certain patients while another may not.

The third point I had to realize was that we do not change a patient's feelings by reasoning with him—there is nothing logical about emotion. We do help him, however, if we accept his illogical emotions as his right and dilute them by helping him realize that many others would feel the same way under similar circumstances.

The question is frequently asked—"How does one get a patient to talk freely about his troubles and innermost feelings?" As to this I would like to quote Dr. Thomas Rennie, Associate Professor of Psychiatry at Cornell University:

"The method to be used is not one of digging for confessions or striving for a complete history such as you might obtain by following an outline. The method is that of creating a special situation in which the patient feels that he is understood, that he has time to talk, that the doctor really hears what he is saying, that he can talk about many personal matters that he has had no previous opportunity to bring out, knowing that his story will be respected as valid material worthy of a doctor's time and interest. That objective, of course, is best attained by creating a sensitive, understanding atmosphere which permits such material to emerge spontaneously from the patient; consequently, the patient will do most of the talking and the doctor will do very little of it, if he is a wise physician. The patient, like everybody else, is seeking a human being who understands him, a human being who stands behind him ready to support him and encourage him and give him insight and understanding. In the wise doctor he finds a human being to whom he may go with his problems, a person who understands and protects him and has a nonpunitive attitude toward him, and who gives him, primarily, the opportunity to talk and talk and to get out of his system many of these emotional matters that he has previously kept bottled up."

Quite often, and especially with patients who do not talk readily, a

very helpful procedure for the detection of conflict is the use of an adjustment inventory which the patient can fill out at leisure. Let me state, however, that adjustment inventories help the doctor but not the patient. What helps the patient is the insight he gains with the help of the doctor.

Until now I have talked about the importance of finding out how the patient feels about himself, his problems, and others, as well as the type of doctor one has to be in order to help the patient. Now, I would like to say a few more words about anxiety, the common denominator of a great many emotional disturbances, and its physical equivalents.

The text books define anxiety as "an unpleasant emotion caused by a conflict of opposing forces." This emotion can either be accompanied by certain physiological changes related to the cardio-respiratory and vaso-motor systems (experienced as palpitation, shallow or rapid respiration, sensation of tightness or lump in the throat, trembling, "fluttering" in the abdomen, and sweaty, flushed or pale skin) or be displaced through certain parts of the body (known as organ neurosis or psychosomatic symptoms). In some, anxiety often manifests itself in compulsive, obsessive behavior and phobias.

For the last two years, I have used the questionnaire prepared by Dr. John Mitchell and published in the Tenth Series of *The Letters of The International Correspondence Society of Allergists.* In this, the patient is asked whether, in addition to the presenting symptoms, he either has or has had fainting spells, nightmares, sleeplessness, restlessness, lump in the throat, conscious heartbeat, indigestion, diarrhea or constipation, itching of the rectum or vagina, frequency of urination, sighing respiration—in short, whether he has had physiological equivalents of anxiety or other organ neurosis and, also whether there has been a childhood history of bedwetting, thumb sucking, nail biting, temper tantrums, destructiveness, phobias and fears. If the patient has or has had many of the above-named symptoms, then a diagnosis of psychoneurosis can be made on positive evidence and not by exclusion of organic factors alone or by intuition.

In describing the tissue findings in allergic diseases, the pathologist talks about certain findings being characteristic of allergy but not pathognomonic; the same thing can be said when we study emotions of an allergic patient. There is a great deal of evidence that his symptoms may have meaning and that we can get from them some understanding of what is going on within the individual.

Some of you may say, "Why not refer the allergy patient with a psychosomatic component to a psychiatrist?" There are many reasons for not doing so. The most important one, however, is the fact that the majority of people still think that there is something the matter with their minds or that we think they are "crazy" when they are referred to a psychiatrist. Secondly, since the first interview is the most impor-

tant one, because it is as much treatment as fact-finding, the patient feels terribly let down if, after he opened up to you and told you everything about himself, you send him to someone else. Thirdly, if you can be the type of doctor I have described, you will be able to help many without a psychiatrist. Occasions do arise, however, and frequently, when I do refer patients to psychiatrists, because some patients require deeper psychotherapy and will not respond to simple ventilation, dilution, and the support from someone they feel is interested in them.

In conclusion, let me say that I am still an allergist. My patients are examined for infection; are still given skin tests, blood studies, and x-rays; and do receive hyposensitization treatment. What I tried to bring out in this paper is that my results are much better; and, as an allergist, I am less frustrated since I have been conscious of my patients as personalities with wishes, fears, hopes, and attitudes toward their parents, husbands or wives, brothers, sisters, doctors, and employers, besides being a collection of organs or having a specific sensitivity to certain substances.

I realize that there is nothing new in this approach—the good family physician has always used it. What I have tried to bring out, however, is that, while in the past it was an intuitive gift granted to a few, now many more of us could study and treat the psychological and allergic factors in their mutual inter-relationship if we would make use of the vast amount of knowledge dynamic psychiatry has accumulated.

The books listed in the Bibliography have been very helpful to me.

BIBLIOGRAPHY

1. Alexander and French: Psychosomatic Medicine.
2. Dunbar, Flanders: Emotions and Bodily Changes. New York: Columbia University Press.
3. Dunbar, Flanders: Psychosomatic Medicine.
4. English-Pearson. Emotional Problems of Living.
5. Hinsie, Leland E.: The Person in the Body.
6. Levin, Maurice: Psychotherapy in Medical Practice. The MacMillan Company.
7. Levy, John, and Monroe, Ruth: The Happy Family. New York: Alfred A. Knopf, Inc.
8. Menninger, Karl: Love Against Hate. Harcourt-Brace & Company.
9. Menninger, Karl: Man Against Himself. Harcourt-Brace & Company.
10. Ribble, Margaret A.: The Rights of Infants. New York: Columbia University Press.
11. Teaching Psychotherapeutic Medicine. New York: The Commonwealth Fund.

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AN UNUSUAL ALLERGIC REACTION TO PENICILLIN

A Case Report

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A REPORT of an unusual reaction resulting in an acute asthmatic attack following the use of penicillin aerosol therapy is presented. The only other report[2] found in the literature is one in which a severe reaction occurred in an asthmatic patient during penicillin aerosol therapy. Aerosol penicillin (40,000 U/c.c.) was given for one hour periods on three successive days of one week. The regimen was repeated the second week. After the third treatment in the second week the patient went into status asthmaticus which was difficult to control.

CASE REPORT

A man, aged fifty-eight, was admitted to the medical service of the Long Island College Hospital with chief complaints of difficulty in breathing, coughing and wheezing.

Past History.—Asthmatic attacks had repeatedly occurred since the age of forty-three. Skin tests to the common allergens had demonstrated positive reactions to the following: dust, feathers, dog epithelium, rice, rye, fish, spinach, string beans, coffee, figs, orange, lemon and grapefruit. With absolute avoidance of all reacting substances, the frequency and severity of his asthmatic attacks were unaltered. He tried change of climate, remaining at Phoenix, Arizona, for six months, in California for another six months, and then in New Mexico for several months, with no effect upon his asthma. He then returned East to his home. In 1937, gastrointestinal x-ray studies revealed a duodenal ulcer and he has been on a modified Sippy Diet ever since. A tonsillectomy was performed in 1937 and the following year all his teeth were removed. There was no evidence of chronic sinusitis or pulmonary disease at that time.

Family History—Irrelevant.

Present Illness.—Immediately previous to the hospital admission he had had an intractable asthma for about two months. Several doses of ephedrine did not afford relief. Repeated injections of epinephrine, intravenous aminophylline and oxygen inhalation also failed to give relief. Five weeks before admission, penicillin aerosol treatment was instituted, three times daily in a concentration of 30,000 units of penicillin/cc in distilled water. Approximately four hours after the first aerosol penicillin treatment he developed a severe asthmatic attack which was relieved by epinephrine. But, at this time, one could not determine whether this was another coincidental attack of asthma or an exacerbation due to penicillin. Penicillin aerosol administered a second time was followed by an asthmatic attack about three hours later. The third penicillin aerosol treatment was again followed by another asthmatic attack about 1½-2 hours later. During the inhalation of penicillin the fourth time, he suddenly developed a very severe attack of dyspnea, choking sensation, cough, marked cyanosis and a semi-comatose state. The dyspnea was so severe and the

From the Division of Allergy of the Department of Medicine, The Long Island College Hospital.
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general condition so alarming that death seemed imminent. These symptoms were controlled with oxygen, subcutaneous epinephrine and intravenous aminophylline. Following these episodes, his chronic asthma was not relieved and he was readmitted to the hospital for further study and treatment.

Physical Examination.—Temperature was 100.4° F.; pulse, 124; respiration, 28; and the blood pressure, 148/102. Examination revealed a fifty-eight-year-old man of average height and slender build. His skeleton was medium in size, muscles light and panniculus, thin. There was a loss of elasticity of the skin and generalized poor muscle tonus. He looked older than his stated years and appeared to be chronically ill. The eyes and ears were negative. The nasal mucous membrane was red and edematous and the septum was deviated to the right. The pharynx was moderately injected, and the tonsils absent. The trachea was in the mid-line. The anteroposterior diameter of the chest was greatly increased. This measurement approximated the lateral diameter. Percussion note was hyperresonant. Breath sounds were asthmatic throughout both lung fields. Coarse expiratory râles obliterated all other sounds. Heart sounds were entirely obliterated by the emphysematous chest and the coarse wheezes. Abdomen was flat. Wrinkling of the skin denoted recent loss of weight. Extremities and reflexes were normal.

Laboratory Examinations.—Urine was normal throughout; blood count revealed nothing except for 3 per cent eosinophiles; sputum, no acid-fast bacilli in direct smear; throat culture, streptococcus viridans, pneumococcus, m. flavus and m. catarrhalis in moderate numbers; sedimentation rate, 17 mm. per hour; vital capacity, 2300 c.c.; venous pressure, 90 mm.; circulation time (Decholin-arm to tongue) 18 seconds; electrocardiogram tracings suggested myocardial damage; roentgenogram of chest revealed increased hilar markings.

Clinical Course.—The patient's asthma was considerably improved with repeated injections of epinephrine, aminophylline and oxygen inhalation. The wheezing disappeared in a few days. Intradermal testing with penicillin in a dilution of 1000 units per cc produced an immediate marked local reaction. The maximum diameter of the wheal and area of erythema was 7 x 4 cms. Also, an erythematous papular eruption appeared over the entire medial surface of the arm. Almost immediately, a severe constitutional reaction took place, characterized by dyspnea, cyanosis, wheezing, and cough which was controlled by repeated injections of epinephrine and aminophylline. Passive transfer to the arms of three other patients was negative.

DISCUSSION

Therapeutically, aerosols are used chiefly to enable a drug to reach the depths of the lungs. The clinical effectiveness of the inhalation of penicillin aerosol in bronchial asthma has been described by Barach[1]. In aerosols the penicillin mist will penetrate the alveoli where a local concentration will be reached which cannot be obtained by intramuscular injection. With penicillin aerosol therapy the Gram-positive organisms disappear and are replaced by Gram-negative organisms. Favorable reports have appeared in the use of penicillin aerosol therapy, notably by Segal[4], Barach[1] and Vermilye[5], with no reactions as described in this paper.

As previously explained, reports of this type of reaction, as presented, are lacking in the literature, except for the one reported above.[2] It is our

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COSMETIC SENSITIZERS

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RECENT activity on the part of the Federal Food and Drug Administration, the American Medical Association, and other organizations toward more rigid control of the manufacturing procedures and the ingredients used in cosmetic preparations has prompted many manufacturers to scrutinize their products.

Since the use of cosmetics has increased so tremendously in the last ten years (816 million dollars being spent in 1948) the number of cases of dermatitis of cosmetic origin has correspondingly increased. In line with these trends and with the rising public interest in scientific achievement, many more persons who might have given up the use of cosmetics ten years ago are now demanding that we do something about their cases. As a part of a continuing study toward the production of better and especially so-called hypoallergenic cosmetics, the authors have reviewed the literature with special attention to that of the past decade for data which might lead to the formulation of less sensitizing products.

It is the purpose of this paper to list many known sensitizing agents which may be used in several cosmetic items and to list references to the literature. Only the most clear-cut cases have been selected. These are to serve as a guide to collaborating scientists in their initial search for new or altered cosmetic formulations.

The first step toward the solution of the patient's problem is to find out which cosmetic ingredient is the offending agent. Many published case histories show that a certain cosmetic is sensitizing, but the author was either unable to trace the exciting ingredient or had no time to do so. Some papers report that the dyes were responsible for sensitivity but they fail to name the dyes. Other papers may give conflicting data concerning certain ingredients as sensitizing agents of a cosmetic item. Of course, this is common with biological data during the early stages of investigation, but it may be due largely to the fact that the investigator has not been provided with full information regarding the materials with which he has been supplied. It is difficult, therefore, for the busy physician to isolate an individual ingredient from an offending cosmetic in order that he may advise his patient what to do so that she may still enjoy the use of cosmetics.

The manufacturer of cosmetics should be willing and ready to supply test kits and specifications of ingredients to the physician. The principal obstacle to this procedure is secrecy. It is believed by some that they may be protected from competition by preserving secrecy. Today this

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is an erroneous opinion except for the secrecy of the "know-how." Scientifically formulated cosmetics as the result of research toward the production of a desired effect, if something new, can probably be patented. (If it is not new and it is good, it will be copied). Research accompanying the formulation period will probably result in a "know-how" that can also serve as some protection. The discriminatory release of formulas to physicians should, therefore, not be dangerous to the manufacturers.

Assuming that test kits for cosmetic ingredients are available or that the formulas for all cosmetic preparations are available to the physician, still other problems arise in the determination of the contact excitant.

1. Will the single ingredient give the same response as when it is incorporated with other constituents?
2. Does the area on which the test is run react the same as the area on which the cosmetic is used?
3. Was some other cosmetic used in conjunction with the suspected sensitizer?
4. Has the test sample been contaminated?
5. Was the offending cosmetic free from all contaminating agents such as mold, bacteria, machine oil, cleaning solvents, and other foreign matter peculiar to the manufacturing area?

Inasmuch as cosmetic allergy usually manifests itself as contact dermatitis without hereditary influence, with no demonstrated reagins or antibodies in the blood and no accompanying eosinophilia, the mechanism of tissue alteration is still a puzzle. All of the above factors, therefore, must be seriously considered by the collaborating physician and the manufacturer. Single ingredients and combinations of two or more ingredients should be tested. The areas taken for patch testing must be carefully selected by the physician based upon his experience with such tests. The physician must record all cosmetics used by the patient according to his routine in establishing the case history so that incompatible cosmetics may be discovered. On the other hand, the manufacturer must supply carefully packaged test samples free from all extrinsic contamination so that the physician can compile accurate data on the sensitivity of his patient. Finally, the manufacturer must supply a finished product made of the highest grade ingredients and made under rigid rules of cleanliness and careful control checking to insure the absence of molds, bacteria and other possible contaminating agents. This is very important because it is common knowledge that the allergens in contact dermatitis range from simple salts to complex chemical structures, and the number can, therefore, run into the thousands. Occasional contact with low concentrations of these highly sensitizing contaminants may cause violent reactions which could brand an otherwise innocuous cosmetic allergenic.

In the accompanying tables the principal sensitizing ingredients of several of the most widely used cosmetics have been listed together with references to the literature.

TABLE I. FACE POWDER

Ingredient	Use	Toxic	Irritant	Sensitizer	Ref.
Aluminum stearate	Adherent	—	—	—	—
Chalk	Absorbent, bloom	—	—	—	—
Kaolin	Absorbent, adherent	—	—	—	—
Magnesium oxide	Opacity	—	—	X	2
Magnesium carbonate	Absorbent, perfume base	—	—	—	—
Magnesium stearate	Adherent	—	—	—	—
Magnesium trisilicate	Absorbent	—	—	—	—
Silica	Adherent, slip	Silicosis	—	—	31, 43
Starch	Absorbent, slip, bloom	—	—	X	44, 50
Talc	Slip	Granuloma	—	—	72
Titanium dioxide	Opacity	—	—	—	—
Tragacanth gum	Binder	—	—	X	11
Zinc oxide	Opacity	—	—	—	—
Zinc stearate	Adherent, slip	—	On inhalation	—	37, 16
Orris root		—	—	X	89, 60
Metallic lakes of aniline dyes	Color	—	—	X	26
Oxides of iron ochres umbers sienna	Color	—	—	—	—

TABLE II. ROUGE

Ingredient	Use
Cake Rouge	
Rice Starch	
Talc	See Face powders
Zinc Oxide	
Zinc Stearate	
Liquid Rouge	
Methyl cellulose	Gel
Sodium alginate	Suspending agent
Cream Rouge	
See cold cream	
pigments and colors	See lipsticks
perfumes	See chart on perfumes

POWDERS

When made from the ingredients listed in Tables I and II, face powders, rouge, dusting powders and talcums are relatively free from danger to the user. Long continued or concentrated exposure by inhalation to those containing silica and zinc stearate may produce dangerous conditions. Talc when used on broken skin may lead to granuloma. Most sensitizing reactions from powders have been traced to perfumes and to the pigments used for effecting the desired shades. In most cases where the pigment has been thought responsible it has been found that in reality the reaction was due to failure of the manufacturer to remove traces of intermediates which were sensitizers.

Face powders can be beset with danger to hypersensitive individuals if the manufacturing techniques, although relatively simple, are not properly controlled. The greatest care should be exercised in cleanliness of equipment and personnel, the selection and handling of ingredients, and the packaging of the finished product. Traces of cleaning solvents, machine lubricants, mold spores, package liners, and other contaminating materials peculiar to the manufacturer's compounding areas are likely to introduce sensitizing agents into an otherwise safe powder.

CREAMS

Plain cold creams and vanishing creams are usually found to have low incidence of sensitization or irritating effects. In both the principal offender is probably lanolin or cocoa butter. Perfume is also a common offender in cold creams. In vanishing creams a faulty formulation may cause irritation due to the improper balance between the basic and acid ingredients.

Lotions, astringents and tonics may contain sensitizing ingredients, most of which have been referred to above. They may also cause irritation due to dehydration or defatting of the tissues to which they are applied.

TABLE III. LIPSTICK

Ingredient	Use	Irritant	Sensitizer	Reference
Beeswax	Body binder	—	X	67, 87
Butyl stearate	Dye solvent	—	—	—
Caranauba wax	Body, rigidity	—	—	—
Castor oil	Dye solvent	—	X	92
Ceresin	Stiffening agent	—	—	—
Cetyl alcohol	Dye solvent, emollient	—	—	—
Cocoa butter	Body (low M.P.)	—	X	91
Diglycol stearate		—	—	—
Glycerine	Solvent for plasticizer	—	—	—
Lanolin	Emollient	—	X	82, 54, 74, 24, 79
Lard	Solvent	—	—	—
Ozokerite	Body (high M.P.)	—	—	—
Paraffin	Body (high M.P.)	—	—	—
Paraffin liquified	Lubricant, gloss	—	X	52, 7, 56, 39
Petroleum jelly	Lubricant	X	X	17, 52, 7, 56, 39
Spermacetti	Emollient (low M.P.)	—	—	—
Stearyl alcohol	Dye solvent	—	—	—
Vegetable oils	Gloss	—	—	—
Tetrabromofluorescein	Dye	—	X	80, 79, 73, 35, 28
Dibromofluorescein	Dye	—	X	80, 79, 73, 35, 28

LIPSTICK

With lipstick the selection of base materials should be subject to rigid specifications. The same rigid controls should exist in the manufacture and handling of materials as should be observed in the manufacture of all cosmetics. For the most part, however, the indelible dyes used in the lipstick appear to be the principal offending agents. Here again it is suspected that the failure to remove all traces of intermediates is largely responsible for the sensitizing effects of the dyes. Such meticulous purification procedures are costly and may be prohibitively so if carried beyond reasonable limits.

Some manufacturers supply lipstick test kits which are available to the physician and which may be used to advantage in tracing offending ingredients. Some of these manufacturers provide special lipsticks made according to the physician's request and thus allow many women to use lipstick who otherwise cannot tolerate any of those available for purchase. Increasing use of such service will enable newer blends to be made for wider use by hypersensitive persons.

NAIL POLISH

For the most part nail polishes are made from a nitrocellulose base into which certain other synthetic resins, principally the phenol formaldehyde

TABLE IV. NAIL POLISH

Ingredient	Use	Sensitizer	Reference
Nitrocellulose	Base	X	57, 12, 46, 23, 21, 58
Ester gum	Gloss, adhesion	X	40, 57
Glycol ether	Solvent, plasticizer	X	58, 92
Formaldehyde resins	Gloss, adhesion	X	53, 57, 58, 75, 30, 46, 23
Alcohol	Solvent	—	92
Ethyl acetate	Solvent	X	92
Toluene	Solvent	X	92
Butyl acetate	Solvent	X	92
Amyl acetate	Solvent	X	92
Butyl alcohol	Solvent	—	92
Dibutyl phthalate	Plasticizer	X	92
Ethyl lactate	Plasticizer, solvent	—	92
Rosin	Gloss	—	92
Dammar	Gloss	—	92
Spruce gum	Gloss	—	92
Copal	Gloss	X	92
Ethyl cellulose	Base	—	92
Mastic	Gloss	—	92
Alkyd resins	Gloss	—	—
Castor oil	Plasticizer	X	92
Methyl ethyl ketone	Solvent	X	92, 30
Polyethylene	Bottle closure	—	92
	Brush stem		
Nylon	Brush bristle	—	92
Vinylite	Bottle closure	X	92
Camphor	Plasticizer	X	92
Santolyte M.S.	Plasticizer	X	92

or the sulfonamide formaldehyde types, plasticizers and a combination of solvents have been blended. There are several contradictory reports upon the effect of the nitrocellulose bases. The prevailing opinion at present is that the synthetic resins used in conjunction with the nitrocellulose are the principal offenders. There is considerable evidence, much of it as yet unpublished, that several of the solvents and plasticizers which are commonly used are responsible for so-called nail polish dermatitis.

The bottle closures and applicators, if not properly selected, may also contain sensitizing agents.

In the tables covering some ingredients that have been tried for the possible formulation of a hypoallergenic nail polish, several known sensitizers have been listed. Most of them were in combination with an ethyl cellulose base and were tried on patients with known sensitivity to common nail polishes. This method, however, rules out effects that might otherwise occur when complex mixtures of the otherwise innocuous single ingredients are used. Many more systematic studies must be made before definite conclusions can be drawn as to the effects of combinations.

HAIR PREPARATIONS

Hair dyes, rinses, and restorers are in widespread use. Many dangerous reactions have resulted from the application of these materials.

For the most part hair rinses are relatively safe for home use in that they consist chiefly of vegetable colors. They impart colors by adherence to the hair rather than by actually coloring the hair shaft.

Hair restorers which have been in use for years depend upon the production of a metallic sulfide by combination of the sulfur of the hair with a metallic salt. The principal danger is the toxic reactions that may occur through careless use of the metallic salts.

TABLE V. HAIR PREPARATIONS, DYES AND RINSES

Ingredients	Sensitizer	Reference
VEGETABLE COLORS		
Henna	X	15
Walnut leaves	X	90
Indigo	X	90
Sage, salvia	—	—
Chamomile	X	63, 76
Camomile		
METALLIC COLORS		
Copper salts	—	—
Bismuth citrate	?	90
Lead acetate	?	86, 88, 90
Nickel ammonium sulfate	X	77
Ferric Chloride	?	90
Manganese acetate	—	—
Silver nitrate	?	86, 90
Pyrogallol	X	86, 3
DYES		
Paraphenylene diamines	X	3, 41, 78
Para toludine diamine	X	90, 51
Aniline dyes	X	93, 90, 26

TABLE VI. HAIR PREPARATIONS, TONICS

Ingredient	Toxic	Irritant	Sensitizer	Reference
Castor oil	—	—	X	92
Pilocarpine	—	—	—	—
Peru balsam	—	—	—	—
Salicylic acid	—	—	X	29
Cocoa butter	—	—	X	91
Lanolin	—	—	X	82, 54, 74, 24
Oxyquinolin sulfate	—	—	—	—
Chloral hydrate	—	—	X	1
Euresol	X	—	—	34
Bergamot	—	—	X	33, 28
Cantharides	—	X	X	42
Resorcin	X	—	X	34, 83, 84, 27
Cinchona	X	—	—	81
Quinine	X	—	X	19, 4, 15, 13
Chlorothymol	—	—	X	71, 70
Capsicum	—	X	—	—
Arsenic	—	—	X	59, 32
Oxycholesterin	—	—	—	—

TABLE VII. HAIR PREPARATIONS, WAVE PREPARATIONS

Ingredient	Irritant	Sensitizer	Reference
Cellosolves	X	—	20, 55
Sulfonated oils	X	—	20
Keratin	X	—	20
Potassium sulfite	X	—	20
Potassium carbonate	X	—	20
Ammonium carbonate	X	—	20
Sodium carbonate	X	—	20
Maleic Anhydride resins	—	X	68, 59
Karaya gum	—	X	26
Acacia	—	X	26
Tragacanth	—	X	26

Hair dyeing is dangerous to say the least. It should never be done except by experts and then only after careful patch testing on the individual on which they are to be used. Many cases of dermatitis, toxic reactions and even fatalities have been reported from the use of hair dyes of new formulation.

Hair tonics and scalp preparations many times contain irritants and

sensitizing agents. These should be suspected when allergic symptoms develop.

Wave sets, eyebrow and eyelash dyes should be used with caution. Some have been reported to have produced disastrous results.

TABLE VIII. PERFUMES

Ingredient	Irritant	Sensitizer	Reference
Linaloa Oil	—	×	86
Cassia	—	×	86
Lavender	—	×	86, 49
Pinene	—	×	86, 45, 8, 66
Orange	—	×	86
Lemon	—	×	86, 45
Bitter Almond	—	×	86
Orris	—	×	86
Ihlang-Ihlang	—	×	86
Bergamot	×	×	33, 25, 49, 64
Synthetic Jasmine	—	×	9
Methyl Heptine Carbonate	—	×	38, 5, 78
Geraniol	—	×	45
Citral	—	×	45

SUMMARY

In summary, we have presented a list of the most common cosmetic ingredients. Many of these have been reported as being sensitizers by the indicated investigators.

We have pointed out that the greatest care should be exercised in the selection of cosmetic ingredients.

We have emphasized the fact that faulty techniques in manufacturing and packaging may lead to the introduction of allergenic materials which may nullify the care taken in the selection of ingredients.

We recognize the difficulties that exist in the tedious screening that is sometimes necessary to establish the identity of a sensitizing ingredient and offer our facilities in whatever way we can aid the allergist.

We believe that by continuous collaborative effort, no matter how difficult and involved a case of cosmetic allergy may appear to be, there is always hope of finding a cosmetic, whether it be a regular product of a hypoallergenic cosmetic house or a special formula, which will not sensitize the patient. The result will be a satisfied patient, added knowledge to the formulating chemists, and new, beneficial products to sell.

REFERENCES

1. Abramovitz, E., and Noun, M.: J. Allergy, 4:338, 1933.
2. Abramovitz, E., and Russo, J.: Arch. Dermat. & Syph., 41:707, 1941.
3. Andrews, G.: Diseases of the Skin. Philadelphia: Saunders Co., 1938.
4. Ayres, S., and Anderson, N.: J. Allergy, 4:146, 1933.
5. Baer, H. L.: Arch. Dermat. & Syph., 32:726, 1935.
6. Beinhauer, L.: Arch. Dermat. & Syph., 41:892, 1940.
7. Berry, H.: Brit. M. Bull., 3:182, 1945.
8. Bingeman: Berlin Theses, 1938.
9. Bloom, D.: Arch. Dermat. & Syph., 42:968, 1940.
10. Bowen: Arch. Dermat. & Syph., 29:506, 1939.
11. Brown, E., and Crepea, S.: J. Allergy, 18:214, 1947.
12. Burgess, J.: Canad. M.A.J., 45:336, 1941.
13. Burgess, J., and Usher, B.: Canad. M.A.J., 23:45, 1930.

14. Carleton, A.: Brit. Med. J., 1:999, 1933.
15. Cole: J.A.M.A., 88:397, 1927.
16. Comm. of A.M.A., J.A.M.A., 84:750, 1925.
17. Cosmetics and Allied Preps., Bureau of Invest., J.A.M.A., 1937.
18. Curtis, G., and Netherton, E.: Arch. Dermat. & Syph., 41:729, 1940.
19. Dawson, W., and Garbade, F.: J.A.M.A., 94:704, 1930.
20. Deakins: Drug & Cosmetic Indust., 41:198, 1937.
21. Dobes, W. L., and Nippert, P. A.: Arch. Dermat. & Syph., 49:183, 1944.
22. Ellis, F. A.: Arch. Dermat. & Syph., 56:801, 1947.
23. Ellis, F. A., and Kirby-Smith, H.: J.A.M.A., 116:45, 1941.
24. Fanburg, S.: Arch. Dermat. & Syph., 42:479, 1940.
25. Fasal, P.: Arch. Dermat. & Syph., 51:163, 1945.
26. Feinberg, S. M., and Shoenkerman, B. B.: Wisconsin Med. J., 39:734, 1940.
27. Flandin, C., Rabeau, H., and Ukrainszyk: Bull. Soc. franc. de dermat. et syph., 42:1804, 1935.
28. Flandin, C., Rabeau, H., and Ukrainszyk: Bull. Soc. franc. de dermat. et syph., 45:928, 1938.
29. Ford, W.: J.A.M.A., 103:483, 1934.
30. Franks, A. G.: J. Allergy.
31. Gardner, L.: J.A.M.A., 103:743, 1934.
32. Gelfand, H.: J. Allergy, 7:254, 1936.
33. Goodman: Am. J. Phys. Therap., 9:16, 1932.
34. Graham, S., and Tisdall, F.: Canad. M.A.J., 12:730, 1922.
35. Hallier, F. F.: Brit. J. Dermat., 49:485, 1937.
36. Harthausen: Acta dermato venereol., 25:527, 1945.
37. Heiman and Aschner: Am. J. Dis. Child., 23:503, 1922.
38. Hoffman, M. J., and Peters, J.: J.A.M.A., 104:1072, 1935.
39. Hollander, L.: Arch. Dermat. & Syph., 38:49, 1938.
40. Holtzman, I.: Arch. Dermat. & Syph., 43:1007, 1941.
41. Ingram: Brit. J. Dermat., 4:422, 1932.
42. J.A.M.A., 76:50, 1921.
43. J.A.M.A., 110:291, 1938.
44. J.A.M.A., 116:2556, 1941.
45. Keil, H.: J. Invest. Dermat., 8:327, 1947.
46. Keil, H., and Van Dyck, L.: Arch. Dermat. & Syph., 50:39, 1944.
47. Keschner and Rosen: Arch. Opth., 25:1020, 1941.
48. Klauder, J., and Hardy, M.: Occupational Med., 1:168, 1946.
49. Lane, J., and Strauss, M.: J.A.M.A., 95:717, 1930.
50. Langer, E.: Urol. & Cutan. Rev., 43:213, 1939.
51. Lawrence, M. W.: J. Invest. Dermat., 8:177, 1947.
52. Levin, S., and Moss, S.: Ann. Allergy, 6:579, 1948.
53. Markuson, K.; Mancuso, T., and Soet, J.: Indust. Med., 12:383, 1943.
54. Milian and Gasnier: Bull. Soc. franc. de dermat., et syph., 43:1473, 1936.
55. Morris, Nelson, and Calvery: J. Pharm. & Exper. Therap., 74:266, 1942.
56. Niles, H. D.: Arch. Dermat. & Syph., 43:689, 1941.
57. Osborne, E. D.; Jordan, J. W., and Campbell, P. C.: Arch. Dermat. & Syph., 44:604, 1941.
58. Palmer, R. B.: Arch. Dermat. & Syph., 44:13, 1941.
59. Plotz, M.: Am. J. Dis. Child., 68:409, 1944.
60. Rackemann, F.: J.A.M.A., 84:489, 1925.
61. Rappaport, B., and Hoffman, M.: J.A.M.A., 116:2656, 1941.
62. Rosenbaum, M.: Arch. Dermat. & Syph., 48:193, 1943.
63. Rowe: J. Allergy, 5:383, 1934.
64. Sandler, I., J.A.M.A., 112:2411, 1939.
65. Satulsky, E.: J. M. Soc. New Jersey, 40:137, 1943.
66. Schmidt: Derm. Wchnschr., 112:389, 1941.
67. Schwartz, L., and Peck: U. S. Pub. Health Rep., 6:14, 1935.
68. Schwartz, L.: Pub. Health Rep., 58:162, 1943.
69. Schwartz, L.: Pub. Health Bull., 215:45, 1934.
70. Schwartz, L., and Tulipan, L.: Occupational Diseases of the Skin. Philadelphia: Lea & Febiger, 1939.
71. Schwartz, Oliver, and Warren: U. S. Pub. Health Reps., 55:1111, 1940.
72. Seelig, M.: J.A.M.A., 123:950, 1943.
73. Sezary, A.; Horowitz, A., and Genet, H.: Bull. Soc. franc. de dermat. et syph., 42:1578, 1935.
74. Sezary, A.; Horowitz, A., and Genet, H.: Bull. Soc. franc. de dermat. et syph., 43:402, 1936.

75. Simon, F. M.: South. M. J., 36:157, 1943.
76. Sternberg, L.: J. Allergy, 8:185, 1937.
77. Stewart and Cormia: J. Allergy, 5:575, 1934.
78. Sulzberger, M. B., and Goodman, J.: J. Allergy, 9:136, 1938.
79. Sulzberger, M. B., and Goodman, J.: Arch. Dermat. & Syph., 37:597, 1938.
80. Sulzberger, M. B., and Hecht, R.: J. Allergy, 12:129, 1941.
81. Sulzberger, M. B., and Kerr, P.: J. Allergy, 4:326, 1933.
82. Sulzberger, M. B., and Morse, J.: J.A.M.A., 96:2099, 1931.
83. Taylor, J.: J. Cutan. Dis., 13:169, 1895.
84. Templeton, H. J.: Arch. Dermat. & Syph., 42:138, 1940.
85. Tzanck and Sidi: Presse Med., 48:5, 1940.
86. Tulipan: Arch. Dermat. & Syph., 38:906, 1938.
87. Umansky, G.: Derm. Wchnschr., 98:177, Feb. 1934.
88. United States Dispensatory, 1947, p. 626.
89. Vaughan, W. T.: Strange Malady, The Story of Allergy. New York: Doubleday, Doran & Co., Inc., 1941.
90. Vaughan and Black: Practice of Allergy. p. 922. St. Louis: Mosby Co., 1948.
91. Vaughan, W., and Fowlkes, R.: J.A.M.A., 105:955, 1935.
92. Whitacre: Unpublished data, authors' files.
93. Wolcott, G.: Arch. Dermat. & Syph., 41:64, 1940.
94. Zakon, S.: Goldberg, A., and Kahn, J.: Arch. Dermat. & Syph., 56:499, 1947.

DISCUSSION

BOEN SWINNY, M.D., San Antonio, Texas: I am sure we all appreciate this authoritative information on the toxic, irritant and sensitizing properties of the various constituents of cosmetics. Also, I am sure we all appreciate the care with which the so-called hypoallergenic cosmetics are prepared. I believe these hypoallergenic manufacturers have done much to clean up the cosmetic industry of this country. For example, one thing we are rarely now seeing is clinical orris root sensitivity.

As scientists, we are interested in whether or not a certain product is a primary irritant or sensitizer, but, practically, we are interested in relieving our patient. If we take a patient off a cosmetic that is producing a dermatitis and she gets well, the result is the same whether it be toxic, irritant or allergic.

I have been rather amazed since the war at the large numbers of patients I am seeing with cosmetic dermatitis caused by the cream-based shampoos and soaps. I should like to ask the essayist what constituent or what property it is of soap and cream-based shampoos that is causing this influx of patients.

Many of the old offenders, such as arsenic, lead, flaxseed and mercury, are being removed from hair tonics and creams, but there still are a few products which contain these. We are still seeing, occasionally, violent dermatitises due, particularly, to the arsenicals and, occasionally, we are seeing asthma or headache due to the flaxseed contained in hair tonics. Also, we are seeing an occasional patient who absorbs enough egg or milk from a shampoo containing these foods to produce symptoms.

SENSITIZERS IN COMMONLY USED COSMETICS

Potassium Arsenate:
Bakers' Hair Tonic
Nixodene

Mercury:
O. K. Beauty Lotion
Stillman's Freckle Cream
Mercolized Wax
Golden Peacock Bleach
Ovelmo

Phenol:
Noxzema

Lead:
Preacher's Hair Tonic

Lanolin:
Wildroot Cream Oil Hair Tonic
Jeris Cream Oil Hair Tonic
Vaseline Hair Tonic

Egg:
Richard Hudnut Egg Shampoo

Milk:
Milky Fluff Shampoo

Flaxseed:
Kreml Hair Tonic

AN INSTRUMENT DEVISED TO PRODUCE PAINLESS SCRATCHES

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THE purpose of this paper is to describe an instrument* which was devised to simplify the task of scratch testing children. Because of the ease with which it produces painless scratches it has also been used on adults scratch tested at the clinic during the past eighteen months.

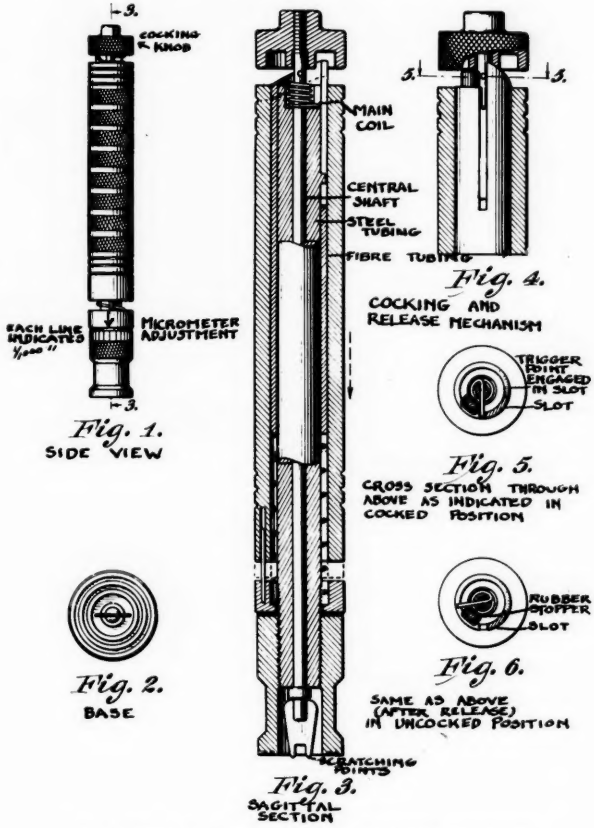

Fig. 1. SIDE VIEW

Fig. 2. BASE

Fig. 3. SAGITTAL SECTION

Fig. 4. COCKING AND RELEASE MECHANISM

Fig. 5. CROSS SECTION THROUGH ABOVE AS INDICATED IN COCKED POSITION

Fig. 6. SAME AS ABOVE (AFTER RELEASE) IN UNCOCKED POSITION

Figs. 1 through 6. Drawings to show mechanical construction.

DESCRIPTION

The entire instrument, about the size of a stubby fountain pen, is composed of a central steel shaft enclosed in a steel tubing which, in turn, is

From the Allergy Clinic, University of Kansas Hospitals.
*Micrometer-Scratcher is the trade name of the instrument.

encased in an outer fibre tubing (Figs. 1 and 3). A steel base is threaded onto the steel tubing to form a micrometer that may be adjusted to allow the instrument to produce a scratch of any desired depth (Fig. 3). At the top of the central shaft is a knob which, when rotated 270 degrees in a clockwise direction, engages to cock the mainspring (Figs. 3, 4 and 5).

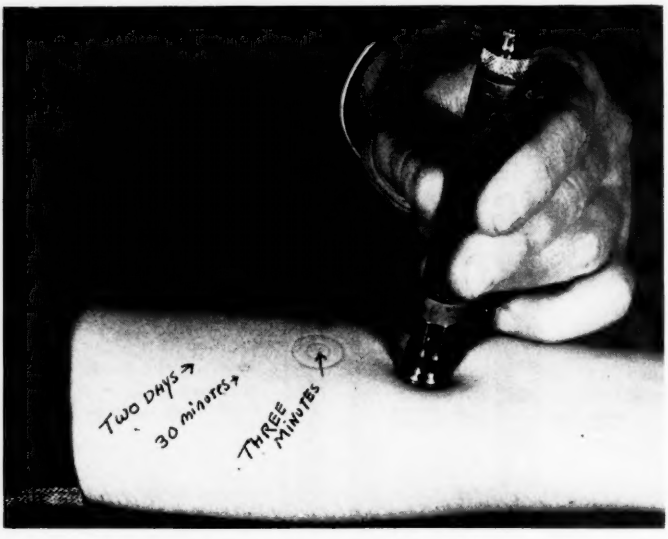

Fig. 7. Photograph showing a scratch being applied and three scratches that have been previously applied at the time indicated.

The bottom of the shaft carries the scratching points made in a single unit of highly tempered nickel-steel (Figs. 2 and 3). When released to rotate, each point moves with great rapidity through an arc of approximately 270 degrees, producing circular scratches 3 millimeters in diameter. A second spring (Figs. 1 and 3) just above the micrometer serves to prevent the release of the trigger mechanism until a skin pressure of approximately 2 pounds is reached. When the trigger mechanism (Fig. 4) is thus automatically released, the central shaft is allowed to whirl rapidly in a counter-clockwise direction. The micrometer is calibrated in units of 1/1000 inch, allowing for the production of scratches 0 to 25/1000 inch in depth; the depth of the scratch remains constant for any given setting. Adjustments finer than 1/1000 inch have been found impractical. Each vertical stripe on the base (Fig. 1) indicates a 1/1000 inch change in the depth of the scratching blades. Rotating the base to the left increases the depth of the scratch; turning it to the right decreases the depth of the scratch. The base or skin contacting surface (Fig. 2) is ridged so that the area of skin being scratched will be held taut. These furrows also serve to identify the location of the delicate abrasion.

TECHNIQUE

Prior to the application of each scratch the cocking knob must be rotated about 270 degrees in a clockwise direction, or until a loud click is heard and felt, which indicates that the device is cocked and ready for use. The instrument is then grasped by its fibre sheath, as one would hold a dart, and pressed against the skin. When a pressure of approximately 2 pounds against the skin is reached, the mainspring will be automatically released, allowing the central shaft to whirl in a counter-clockwise direction. The depth of the abrasion will depend upon the setting of the micrometer. Once the depth of the scratching points has been set it is usually unnecessary to readjust them unless a very delicate or unusually coarse skin is encountered.

ADVANTAGES

The three chief advantages of the instrument may be listed in decreasing importance as follows:

The scratch is painlessly produced, unless it is too deep. Scratches deep enough to draw blood have at times been accidentally produced over bony prominences, especially in the case of thin individuals.

It produces a scratch of the same length and the same depth whether applied by the expert or the novice, thereby minimizing the human element.

The depth of the scratch may be varied to correspond with the texture of the individual skin.

SUMMARY

The instrument described in this paper is capable of producing painless scratches that are consistently uniform in length and depth. The depth of the scratching points may be regulated to within 1/1000 inch. The device makes possible the application of uniform scratches by the assistant untrained in the art of consistently applying uniform scratches in the conventional manner.

METEOROLOGIC FACTORS

(Continued from Page 644)

unfavorable weather condition observed is dampness, most people are convinced that moisture is the cause of their inhalant allergies.

REFERENCES

1. Durham, O. C.: Chapter on pollens and hay fever. Feinberg, S. M.: In Allergy in Practice. Chicago: Year Book Publishers, 1948.
2. Federal Security Agency: Public Health Service. Acosta Ex., 6300 Ext., 6372, (Oct. 14) 1949.
3. Heise, H. A., and Heise, E. R.: The distribution of ragweed pollen and alternaria spores in the upper atmosphere. J. Allergy, 19:403, 1948.
4. Heise, H. A., and Heise, E. R.: The influence of temperature variations and winds aloft on the distribution of pollens and molds in the upper atmosphere. J. Allergy, 20:378, 1949.

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AN EVALUATION OF PERAZIL IN ALLERGIC RHINITIS

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AFTER several years' evaluation of various antihistaminic agents it would seem self-evident that except for some differences observed by individual investigators as to percentages of effectiveness and toxic side effects, almost all of us would subscribe to the fact that whereas one drug is effective in one individual, another in a second, and still another in a third, there is basically, from a clinical standpoint, very little else to recommend one drug more than another.

During the hay fever season of 1949, we undertook to evaluate clinically another newer antihistaminic drug,* which purportedly[1,2] had two outstanding advantages over those previously available—namely, a definite longer duration of effect and minimal side reactions. Following the results observed during that season, it was felt that evaluation in non-seasonal rhinitis might also be of considerable value, and therefore its study was continued for many months beyond the ragweed season.

The patients with seasonal pollenosis, with few exceptions, were all undergoing hyposensitization therapy and were instructed to take the medications only if and when they were experiencing difficulties and, if necessary, to repeat the dose as often as three times daily. Each patient was given a sheet to fill out, indicating the number of tablets taken and the hour of medication, any side effects experienced, and the degree, if any, of relief obtained.

A total of 181 patients were studied, of whom ninety-five had seasonal pollenosis and eighty-six non-seasonal rhinitis. Those with seasonal pollenosis took an average of four tablets a week, and at this time we had a moderately severe ragweed hay fever season. Frankly, we felt that this was a remarkable record, in view of the fact that the next closest drug required a dose 50 per cent greater. A few of these patients were physicians, and invariably their comment was that one tablet seemed to be effective for fully twenty-four hours. Of course, lay patients made no such observations, but the mere fact that so few tablets were ingested would seem to indicate that the benefits were of considerable duration.

In the general evaluation, we separated the seasonal from the non-seasonal cases, since those in the former group could be assumed to have similar exposures to causal allergens.

Table I shows ninety-five patients with ragweed hay fever, of whom forty-one were children under eighteen years of age and fifty-four were adults. Of this total six reported no relief of symptoms whatsoever, fifty reported a fair degree of relief (this we feel is naturally equivocal),

*Perazil—Supplied by Burroughs Wellcome & Co.

TABLE I. RESULTS WITH PERAZIL IN POLLEN HAY FEVER

Number Patients		DEGREE OF RELIEF				Number Tablets (1 week)	SIDE REACTIONS				
		None	Fair	Good	Excellent		Severe Drowsiness	Nausea	Vomiting	Diarrhea	Headache
Children	41	2	20	7	12	191	6	1		1	1
Adults	54	4	30	8	12	194	10	1	2	1	1
Totals	95	6	50	15	24	385	16	2	2	2	2

TABLE II. RESULTS WITH PERAZIL IN NON-SEASONAL RHINITIS

Number Patients		DEGREE OF RELIEF				SIDE REACTIONS				
		None	Fair	Excellent	Dosage	Severe Drowsiness	Severe Headache	Mild Headache	Mild Nausea	Mild Drowsiness
Children	52	7	22	23	50mg B.I.D.				1	2
Adults	34	4	10	20	50mg B.I.D.	3	1	2	1	4
Total	86	11	32	43		3	1	2	2	6

fifteen reported good relief, and twenty-four reported excellent results. The onset of relief varied from thirty minutes in thirty-three patients, to longer than one hour in twenty patients. An average of 385 tablets were taken by these patients in one week's time, making an individual average of four tablets for each patient each week. No patient took more than two tablets in any one day. The side reactions varied from severe drowsiness occurring in sixteen individuals, to mild nausea and headaches in each of two individuals, and vomiting and diarrhea in one. The incidence of side effects was therefore 23 per cent. On the other hand, eighty-six patients with non-seasonal rhinitis were instructed to take two tablets daily, one in the morning on arising and the other at 6:00 p.m. unless side reactions were such as to necessitate discontinuance. Of this total, four had to discontinue the drug because of the severity of the side effects; ten others had mild side effects such as drowsiness, headache, and nausea.

Table II gives the detailed breakdown of these cases. Side effects here were manifested in 16 per cent of the patients.

Combining the two series of figures, we then had 181 patients on this drug, with side effects occurring in nearly 20 per cent of the cases. In evaluating effectiveness we might consider those reporting fair results as equivocal and disregard them, in which case the figures for effectiveness would be approximately 45 per cent. Although nothing outstanding can be noted about the effectiveness or low incidence of side reactions with this drug, we do feel that its longer duration of effect is one to merit consideration; even effectiveness and incidence of toxic side effects compare favorably with other antihistaminics on the market.

(Continued on Page 712)

THE PREVENTION OF INFECTIOUS ASTHMA

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IN a survey of the estimated prevalence of specified chronic diseases in the United States, 1937,[17] asthma and hayfever are *fourth* in number of cases, being outnumbered only by rheumatic diseases, heart disease, arteriosclerosis and hypertension. However, if the number of cases of chronic bronchitis and sinusitis are added to the asthma and hayfever group, they then become second, being outnumbered slightly by rheumatic diseases many of which are also due to infectious agents and bacterial allergy.

The prophylaxis of asthma is a most important phase in its management, yet great pessimism is widely prevalent in the practice of its prevention, particularly of the infectious types. This has led to frequent failures and given many a sense of defeat. The elimination of the allergic factor, hyposensitization, general medical measures and good hygiene must be practiced, but in spite of these, infectious asthma is often not prevented. It is well known that many asthmatic seizures are precipitated or are entirely caused by upper respiratory infections. To date, no prophylactic measures outside of the aforementioned plus removal of foci of infection and climatic change have been used in infectious asthma. These measures have been of some benefit to a fair percentage of patients but they have not been of value in many instances. Injections of vaccines in infectious asthma have benefited enough patients so that they continue to be used. However, the results of vaccine therapy are not uniform, the dosage is a most individual problem, and no general conformity is possible. Skin response to vaccines is unreliable, and therapeutic results are unpredictable and often hazardous. Whereas, one individual may be able to withstand an injection of several thousand million organisms with impunity, another may be incapacitated with severe asthma or other general reactions with an injection of several hundred organisms or less.

Being aware of the remarkable results obtained in the prevention of rheumatic fever,[2,4-6,8,13-16,18-20] and of the greatly reduced incidence of upper respiratory infections particularly of the streptococcal, pneumococcal, and meningococcal groups with sulfonamides,[1,3,7,9-12] an attempt was made to use these drugs in the prevention of infectious asthma.

Reviewing some of the literature pertinent to the prevention of rheumatic fever and upper respiratory infection, it is striking to note the success obtained in tremendous large scale case reports. Coburn and Moore, Thomas and France, France and Reichsman, Caroline Thomas,[14] Norman

Read at the meeting of the Philadelphia Allergy Society, October 12, 1949.

Boyer,[2] Robert Feldt,[6] Charles Connor,[4] and others, attest to the excellent results with sulfonamide prophylaxis in rheumatic fever. Studies made at the Irvington House Sanitarium showed that only one of a group of fifty-four on sulfonamide prophylaxis developed "strep" pharyngitis, whereas in a control group of fifty-four, thirty cases developed "strep" pharyngitis with subsequent manifestations of rheumatism in fourteen after a latent period of three to twenty-one days. In an Army Air Force Rheumatic Fever Control Program under Col. W. P. Holbrook[8] there was a 50 per cent to 75 per cent reduction of incidence of respiratory disease and "strep" infection by the use of sulfadiazine prophylaxis. No serious drug reactions were encountered. Coburn,[3] of the Navy, in 1944 reported on 30,000 men given sulfadiazine continuously in doses of 0.5 gm. daily from December, 1943 to April, 1944. Hemolytic "strep" infections were prevented in 85 per cent. Constitutional reactions occurred in .01 per cent. C. B. Thomas[15] advocated sulfadiazine 0.5 gm. twice daily for five years or more to prevent recurrences of rheumatic fever. She showed that these children suffered no longer from most bacterial infections although they may develop the common cold in mild form, influenza and virus diseases of childhood. Captain R. G. Hodges[7] found sulfadiazine very effective, as a prophylactic drug against streptococcal and pneumococcal infections as well as against rheumatic fever and other respiratory diseases. Toxic reaction danger is small as shown by the U. S. Navy program. Mild reactions as transient skin eruptions developed in 0.3 per cent to 0.6 per cent while serious reactions as exfoliative dermatitis and agranulocytosis were exceedingly rare among the five hundred thousand men given sulfonamide prophylaxis for six months. The reports on the preventive effects of sulfonamides in respiratory diseases comprises hundreds of thousands or perhaps over a million cases with rather remarkable effects and with an astounding low incidence of serious reactions. W. H. Oatway, Jr.,[9] found that after treatment of chronic bronchial infections with sulfonamides that freedom from symptoms remained by giving 0.5 gm. sulfadiazine t.i.d. B. W. Billow and M. S. Albin[1] reported on the efficacy of sulfonamide prophylaxis in the decline of upper respiratory infection, rheumatic fever, lobar pneumonia, atypical pneumonia and absolute prevention in meningitis in twenty thousand soldiers who received one gram daily for five weeks. Two cases of meningitis appeared two weeks after the sulfonamide prophylaxis was discontinued. H. Rusk[10] and M. Siegel[11,12] have added contributions to the literature on the use of sulfonamides in respiratory tract infections.

With this tremendous clinical background we undertook to study the value of sulfonamides in the prevention of infectious asthma. Although only twenty cases are reported of the patients selected for this study, those chosen were patients who had recurrent or perennial infectious asthma or bronchitis who failed to respond to medical, rhinological, bron-

choscopic or allergic management. Drug and vaccine therapy were of minor value. Climatic change was of no prolonged benefit. Although antibiotics relieved many of these individuals during acute episodes and reduced the seriousness and the course of their infection, the chronicity of the disease often remained for long periods and asthmatic recovery was slow. We felt the prevention of infectious asthma was much to be preferred over the treatment. Generally one gram of equal parts of sulfadiazine and sulfamerizine was given daily in two doses to patients weighing over 100 pounds and under sixty years of age. (Only 0.5 gm. daily was given to those under 100 pounds and over sixty years of age.) Most patients were started October, 1948, a few as early as September, and several in November. The dose was cut to 0.5 gm. daily after April 15, 1949, and continued as such until June 1, 1949. Vaccine therapy plus other allergic and general measures were continued although they had been of apparently minor benefit before. Penicillin was considered as a prophylactic, but since the clinical background of the sulfonamides was so much more extensive in prophylaxis, we decided in their favor especially when we considered that penicillin might be needed for infection that might arise during sulfonamide prophylaxis. As the experiment turned out, penicillin was not needed but in one instance in a patient who discontinued the sulfonamides for over six weeks. However, as evidence is gathered penicillin may well be the drug of choice in future prophylactic experiments.

The patients were given 0.5 gm. of sulfadiazine-sulfamerazine mixture twice daily and instructed to drink one glass of water with each dose. Several patients also took 10 grains of soda bicarbonate with each dose. Only one patient experienced a rash, but she was also sensitive to phenobarbital and iodides which she was taking concurrently. Three patients who stopped the sulfonamides for several weeks experienced a recurrence of their asthma following an acute upper respiratory infection. The others who continued sulfonamide medication continuously had no serious breakdowns even with upper respiratory infections. After several days the upper respiratory disease subsided without manifestations of severe asthma.

The time loss from work or school with this procedure was not longer than three days in any case, whereas in previous years these same individuals were incapacitated with asthma from ten days to six months as an aftermath of acute respiratory infections.

To demonstrate the striking benefits obtained from sulfonamide prophylaxis the following case reports are offered.

Case 1.—L. K., a young girl, aged seventeen, suffered from severe asthmatic seizures and yearly attacks of status asthmaticus for the past ten years, being hospitalized for oxygen therapy at least once every year between the months of October and May. She has been under competent medical and allergic management all this

time. A sojourn to Florida was of no benefit since she developed status asthmaticus there that required hospitalization. Her general health and physical development were under par as a result of her frequent severe seizures. In addition to allergic management sulfonamide prophylaxis was started October, 1948, and continued daily until June 1949. No severe attacks of asthma occurred although she developed three "colds." Mild wheezing appeared with these colds but were relieved by ephedrine. The "colds" lasted no longer than three days. No time loss from school was necessary throughout the year.

Case 2.—D. R., aged thirty-seven, experienced attacks of asthma for the first time four years ago although he was subject to frequent "colds." He had recurrences of severe asthma every winter. Status asthmaticus occurred in the winter of 1947 to 1948. He was hospitalized and received five million units of penicillin with some relief but was totally incapacitated for over six months. Hyposensitization with dust and vaccine often precipitated an attack of asthma. Although allergic treatment was continued with minute doses of dust and vaccine, his response was poor. He was placed on sulfonamide prophylaxis from September, 1948, to June, 1949. In the interim he has been employed, with no severe seizures of asthma. Several colds that occurred were transient and any asthmatic symptoms that followed were mild. Epinephrine inhalation which had been used several times daily prior to sulfonamide prophylaxis was not used more than three or four times throughout the eight-month period, and then was used more as a precaution in this man's fear of asthmatic recurrence.

Case 3.—M. P., a man, aged seventy-seven, has had chronic asthmatic bronchitis and hay fever for twenty years. His hay fever had been controlled excellently for the past five years. In the past seven years he was incapacitated at least once every winter with an acute respiratory infection that developed into severe asthmatic bronchitis or pneumonitis. Each attack was severe and prolonged, and occasionally was complicated by auricular fibrillation. Although penicillin shortened the course of these attacks, weakness and chronic asthmatic bronchitis remained for months. Sulfonamide prophylaxis was started October, 1948. He went through the entire winter with no attacks of asthmatic bronchitis or pneumonitis even on 0.5 gm. sulfonamide mixture daily.

Case 4.—E. C., a young woman, aged thirty-three, had severe asthmatic seizures of prolonged duration (several months) every fall and winter. Although she improved on allergic management which included dust and vaccine therapy, she had severe attacks of asthma with every upper respiratory infection. Sulfonamides were given and no asthmatic attacks occurred from October, 1948, to February, 1949. For some reason she stopped the sulfonamides and within three weeks an acute asthmatic seizure was precipitated by a "cold." After being brought under control sulfonamides were again given prophylactically and she has been well since.

Case 5.—C. C., a man, aged thirty-one, had severe attacks of asthmatic bronchitis as a yearly winter occurrence for the past four years. In spite of medical management his asthma started earlier and ended later every year. Sulfonamide prophylaxis was initiated in October, 1948. He was well until March when he discontinued the sulfonamides for economic reasons. Within three weeks asthmatic seizures persisting for eighteen days followed a "cold." After this bout he was again placed on sulfonamides with no further asthma.

Case 6.—W. D., a man, aged forty-eight, had yearly recurrent attacks of asthmatic bronchitis or pneumonitis. Although he responded well to penicillin and bronchodi-

lator drugs, he was often acutely ill and lost several weeks of work every winter. Sulfonamide prophylaxis was instituted in October, 1948. He has had no severe seizures and has lost no time from work this year.

These few case reports demonstrate the effectiveness of sulfonamide prophylaxis in infectious asthma particularly in those uncontrolled by other measures. We are well aware that many cases of infectious asthma are controlled by other procedures, but in those not controlled this has been a most effective prophylactic measure. We are not advocating mass sulfonamide prophylaxis for respiratory infections or where allergic, medical or other therapy has been effective. But we definitely feel that sulfonamide prophylaxis (or other antibiotic prophylactic measures that may be warranted in the future) is of value in those cases of recurrent infectious asthma or bronchitis that are not prevented by allergic or other types of management. Allergic and medical measures however must be continued and with the addition of sulfonamides previous failures are converted into success with gratifying results to the patient and the doctor.

SUMMARY

1. Twenty patients with regularly recurrent infectious asthma and/or bronchitis who failed to respond to allergic or other treatment were given sulfonamide prophylaxis for periods of seven to nine months.

2. No severe attacks of asthma or bronchitis occurred in any who took the prophylactic treatment faithfully.

3. No general reactions occurred. One case of skin eruption appeared in a patient who was sensitive to other drugs.

4. This method of prophylaxis is recommended for the prevention of infectious asthma in those patients who have recurrent attacks of asthma caused by respiratory infections for which other methods of treatment have failed.

5. Allergic and medical management should be continued along with sulfonamide prophylaxis.

BIBLIOGRAPHY

1. Billow, B. W., and Albin, M. S.: Observations on mass chemo-prophylaxis with sulfadiazine. Ann. Int. Med., (May) 1946.
2. Boyer, Norman: Prophylaxis in rheumatic fever. New England J. Med., (April 22) 1943.
3. Coburn, Alvin: The prevention of respiratory tract bacterial infections. J. Am. M. A., (Sept. 9) 1944.
4. Connor, Charles: The diagnosis and management of rheumatic fever. Bull. Northhampton County M. Soc., (Oct.) 1946.
5. Cunningham, T. O.: The sulfonamides. Rocky Mountain M. J., (March) 1943.
6. Feldt, Robert: The prevention of rheumatic heart disease. Wisconsin M. J., (Oct.) 1942.
7. Hodges, Richard: The use of sulfadiazine as a prophylactic against respiratory disease. New England J. Med., (Dec. 21) 1944.
8. Holbrook, Paul: The Army Forces rheumatic fever control program. J.A.M.A., (Sept. 9) 1944.

9. Oatway, W. H., Jr.: Sulfonamides in treatment of chronic bronchial infections. Arizona Med., 1:194-197, (July) 1944.
10. Rush, Howard: Sulfadiazine in respiratory tract infections. J.A.M.A., (June 19) 1943.
11. Siegel, Morris: Studies on the control of acute respiratory infections. J.A.M.A., (July 4) 1942.
12. Siegel, Morris: Studies on the control of acute infections of the respiratory tract. Am. J. Dis. Children, (Aug.) 1945.
13. Sullivan, Francis: Crippled children without crutches. Hygeia, (March) 1947.
14. Thomas, Caroline: The prophylactic use of sulfanilamide. J.A.M.A., (Feb. 15) 1941.
15. Thomas, Caroline Bedell: Prevention of recurrences in rheumatic subjects. J.A.M.A., 126:490-495, (Oct. 21) 1944.
16. Waddill, Franklin: Clinical manifestations of acute rheumatic fever. Virginia M. Monthly, (June) 1939.

* * *

17. National Health Survey Bulletin 6, Sickness and Medical Care Series. United States Treasury Department, Public Health Service, 1938.
18. Sulfanilamide May Prove Rheumatic Preventive. Science News Letter, February 22, 1941.
19. The Prevention of Steptococcal Upper Respiratory Infections and Rheumatic Fever Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide. American Heart Association, October, 1943.
20. The Prophylactic Use of Sulfanilamide in Rheumatic Subjects. Medical Clinics of North America, May, 1940.

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AN UNUSUAL ALLERGIC REACTION TO PENICILLIN

(Continued from Page 669)

belief that these reactions occur more frequently than the search of the literature indicates. These reactions are manifestations of sensitivity to penicillin itself and not to impurities in the penicillin solvent. Penicillin has an amino-acid like structure and can act as an allergen just as any other allergen. It is possible that penicillin itself may also act as a hapten in combination with body proteins as a sensitizing agent. It was demonstrated by Chow and McKee,[3] that there could be a combination of penicillin and serum albumen producing a penicillin-protein combination complex.

REFERENCES

1. Barach, A. L.: Penicillin aerosol therapy. Am. J. Med., 1:268, 1946.
2. Bissell, F. E.: Reaction to penicillin. J.A.M.A., 132:12, 1946.
3. Chow, B. F., and McKee, C.: Science, 101:67, 1945.
4. Segal, M. S.: Inhalation therapy. New England J. Med., 230:456, 1944.
5. Vermilye, H. N.: Aerosol penicillin in general practice. J.A.M.A., 129:250, 1945.

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ALLERGY TO CASTOR BEAN DUST WITH REPORT OF A CASE

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THE explosive suddenness with which a susceptible individual may react to castor bean dust and the severity of the resulting symptoms places this substance in a position of importance as an allergen. The allergic consequences, particularly if the causal agent is not recognized or if proper treatment is not instituted, make it a very dangerous allergen in those industries and occupations in which exposure to it is unavoidable.

According to Feinberg[5] (1946) the most important product of the castor bean is castor oil, which is used for medicinal purposes, chiefly as a cathartic. However, castor oil is also widely used as a lubricant; in the manufacture of artificial leather; for leather dressing; as a varnish ingredient; in the preparation of perfumed oils, hair dressing, lipstick, and other cosmetics; as an ingredient of rotogravure ink and other dyes; and for the manufacture of plastics. Castor bean meal, the residue remaining after extraction of the oil, is in considerable demand.

According to Ratner and Gruehl[8] (1929), the manufacturing process consists of extracting the oil from the castor bean by compression, which leaves a residue or cake. This cake is then ground or pulverized to form, what in the trade is known as, castor bean "pomace." This pomace, because of its high nitrogen content, makes it a very desirable fertilizer. Commercially, it is sacked and sold for this purpose.

From a chemical study, Osborne, Mendel and Harris[7] (1907) concluded that the castor bean contains proteins of the same character as other oil seeds, namely, a considerable quantity of crystallizable globulin, proteoses, and a smaller amount of coagulable albumin. They ascribed the toxic action of the castor bean to the protein fraction, which is an albumin coagulable at 60 to 70 degrees.

Stillmark[10] (1888) showed that the castor bean fraction without the oil has the property of hemolyzing and agglutinating the red blood cells, *in vitro*, of nearly all warm-blooded animals. He gave it the name "ricin." This substance has since been proven to be a toxalbumin and to rank among the most powerful of vegetable poisons.

Bernton[3] (1923) commented that the toxic action of the castor bean is well known and that the ingestion of the whole bean, accidental or otherwise, or even the ingestion of castor oil for medicinal purposes, on occasions, has had dire results.

Sollmann[9] (1936), in his discussion of ricin, states:

"This toxin is contained in the castor seeds but does not pass into the oil. The ricin is responsible for the toxic effects on eating the castor seeds; five or six of these are fatal to a child; twenty to adults; three or four seeds may cause violent gastro-enteritis with nausea, headache, persistent vomiting, colic, sometimes bloody

diarrhea, thirst, emaciation and great debility. The symptoms usually do not set in until after several days. More severe intoxications cause small frequent pulse, cold sweat, icterus and convulsions. Death occurs in six to eight days from the convulsions or from exhaustion. The fatality is about 6 per cent. This small fatality is due to the destruction of the poison in the alimentary canal. The *treatment* would be evacuant and symptomatic. Three to ten days are required for complete recovery."

Sollmann states that a preparation of ricin has been obtained which is a typical albumin and which is so active that 0.0005 mg./kg. is fatal to rabbits. The fatal dose to man would therefore be about 0.035 mg. or 1/2000 grain. This was first shown to be so by Osborne, et al[7] (1907). Sollmann also states that ricin has a very powerful agglutinating action, *in vitro*. Leukocytes, epithelial and other cells are agglutinated. The presence of serum hinders the agglutination.

It is well known, of course, that Ehrlich[4] (1891) did some of his basic work with ricin. He found that injections of this phytotoxin produces an antitoxin (antiricin), and that an animal so treated can survive the injection of 5000 ordinary fatal doses or ricin. Immunity starts in five to six days and lasts for six or seven months. The antiricin is contained in the pseudoglobulin fraction of the serum and contains antitoxin, antiagglutinin and precipitin.

The castor bean meal is fraught with danger for man and beast. When used as a fertilizer, either alone or combined with fodder, it may poison cattle. Exposure to its dust may result in irritation of the conjunctival, nasal, oral, pharyngeal, laryngeal and bronchial mucous membranes. The skin may also be affected. Therefore, those who come in contact with the castor bean or its dust—those engaged in the manufacture of castor oil, or in the packing and shipping of the meal, or as farmers or gardeners—should be warned of its potential dangers.

Bernton[3] (1923) reported a case of castor bean allergy in a research chemist who, in the course of his duties, had been exposed to castor bean. His allergic manifestations included asthma and rhinitis. There had never been any personal or family history of allergy. This patient was subjected to a complete and thorough investigation. Not only was he tested qualitatively but also quantitatively. When he was tested for the degree of his sensitivity to castor bean meal, a cutaneous reaction was obtained with a drop of a 1:250,000 dilution of the protein solution of the meal.

Figley and Elrod[6] (1928) investigated an "asthma colony" in Toledo, Ohio, and found that the condition was due to castor bean dust emanating from a neighboring castor oil factory. The incidence of asthma in the "colony" was in direct proportion to the amount of exposure to castor bean dust but not to the personal and familial allergy history prior to the exposure. They described the castor bean dust as being relatively odorless when compared, for example, to the fumes of linseed oil or flaxseed.

On microscopic examination, they found the particles of the castor bean dust to be the same size as ragweed pollen. The weight of the dust was exactly the same as that of a given amount of pure giant ragweed pollen. This, of course, would explain the ease with which wind carries this dust.

Figley and Elrod did not attempt any desensitization in their series of cases but when they tested two persons, who had given delayed reactions to scratch tests, intradermally using 0.01 cc of 1:1000 extract of castor bean dust they obtained severe inflammatory reactions with widespread aseptic lymphangitis of the entire arm which prostrated these two patients for several days. Subsequently, however, these patients did not suffer with asthma for a period of several weeks even though they lived close to the castor oil mill and had had almost continuous asthma before. Their neighbors who were asthmatic from the same cause and who were not "treated" continued to have symptoms. The authors point out that the asthma in their cases was a specific allergic reaction to the castor bean dust, rather than a toxic one due to irritation and prolonged contact.

Ratner and Gruehl[8] (1929) reproduced the specific clinical picture of anaphylaxis in the guinea pig with the same materials which brought it about in human beings. They showed that the toxic element, ricin, could be clearly differentiated from the allergic element.

Barnard[1] (1930), in a report of seven patients who were sensitive to castor bean extract, stated that he was able to remove the ricin present in the extract without altering its activity.

Bennett and Schwartz[2] (1934) reported two cases of acquired castor bean dust sensitivity which was characterized by sneezing, coryza, itching eyes, cough and wheezing respiration. One patient also developed urticaria of the face, neck and hands. The authors stress that caution must be observed in testing with castor bean dust extract. They state that although other potent extracts such as horse dander, horse serum, rabbit epithelium, cottonseed, pollen and fish are tested with high dilutions, castor bean extract requires still higher dilutions for testing in order to avoid constitutional reactions.

CASE REPORT

The following case presents additional evidence that castor bean meal or dust is a most potent allergenic substance and should continue to be regarded as such.

On July 20, 1949, M.C.N., an adult, male Negro, was referred for allergic consultation. His occupation at that time was that of truck driver and general helper for a landscape and gardening firm. His present illness began on July 14, 1949 when at about 3:30 p.m., while spreading and distributing some fertilizer (which subsequently proved to consist of castor bean meal) on a lawn in the performance of his work, the wind suddenly shifted and blew the meal into his face and body. Fifteen to twenty minutes later his eyes began to smart, itch and tear. His nose felt itchy, and he sneezed in barrages. The exposed skin of his face, neck, ears, and

arms began to burn and itch. He stated that by the time he arrived at the doctor's office his throat had become swollen and sore and his nose so stuffy that he could hardly breathe and he felt as if he was choking. He had developed welts all over his exposed skin where the meal had come in contact with it.

The referring physician stated that when first seen by him, the patient had a severe urticarial eruption on his face, neck, and arms, was in rather severe distress with dyspnea, coughing and wheezing, and complained of choking with a tightness in his mouth, nose and throat. His eyelids were edematous and his conjunctivae were injected, swollen and chemotic. His lips were puffy, and the mucous membranes of his oropharynx were edematous throughout.

Emergency treatment was given in the form of epinephrine injections, antihistaminic drugs by mouth, and calcium gluconate intravenously. He soon experienced some relief of his general symptoms and was referred to an opthalmologist who prescribed Antistine (℞) and butyn eye drops and wet, boric acid compresses. He continued to use the local eye medication and to take the antihistaminic drugs by mouth. His symptoms began to abate, but four days later, he was re-exposed to the meal in trying to obtain a sample for investigative purposes. He insisted that the material be placed in a paper bag by someone else and that he carry it at arm's length. Nevertheless, all of the foregoing symptoms recurred, and he again required epinephrine injections for relief.

When the patient was seen two days after his second exposure, he was not in extreme distress but did appear to be ill. Detailed questioning elicited no personal or family history of allergy. Physical examination revealed a well-developed, male Negro, twenty-nine years of age, 72 inches tall and weighing 178 pounds. His oral temperature was 99.4 degrees, pulse 76 and blood pressure 126/84. His face was swollen and the skin on his cheeks, eyelids, lips, ears and neck was somewhat edematous. There was no urticaria. The conjunctivae and scleras of both eyes were markedly congested. There was lacrimation and photophobia. The nasal mucous membranes and turbinates were red and edematous. The faucial inlet, including the uvula, as well as the posterior pharyngeal wall, was inflamed. The airway, in general, seemed adequate. Pulmonary findings, including fluoroscopy, were not significant. Cervical adenopathy was present. The remainder of the physical examination revealed no pertinent information.

On July 21, 1949, he was patch-tested on the flexor surface of the right forearm with dry castor bean meal and with castor bean meal moistened with normal saline. The patient was warned that if any burning or itching took place underneath the patches he was to remove them immediately, notifying the physician. The burning and itching occurred in about twelve hours, and the patient removed the patches but, unfortunately, because it was about 2 a.m., the patient, out of consideration, failed to call at that time. When he reported about twelve hours after he had removed the patches, he stated that upon removing them he noted a welt about the size of a quarter at the site of the dampened meal. By careful questioning, it was concluded that at this site he must have had a wheal about 2½ cm. in diameter with pseudopodia, surrounded by erythema. At the site where the dry meal had been placed there could still be seen a papular eruption with several of the papules coalesced into one raised area, roughly 1 cm. at the greatest diameter, surrounded by a faint rim of erythema. The patient remarked that at the time he had returned for the sample of fertilizer some of it must have fallen on his arm because he had a few little "spots" which looked exactly like the papules which were present under the dry meal. Even though over seventy-two hours had passed, I could see, upon close examination, residual papules at the locations which he pointed out to me. These, as well as those at the area of the dry meal application, persisted in burning and itching even after three days, particularly when he perspired.

On July 23, 1949, using 1/20 normal sodium hydroxide as a control and as a diluent, scratch tests were performed to castor bean meal dust; pollens of ragweed, grass and plantain; inhalants, including dust, cat epithelium, dog epithelium, horse dander, horse serum, chicken feathers, goat epithelium, pyrethrum, orris root, glue, wool, cottonseed, flaxseed, kapok, silk and tobacco. Within fifteen minutes after the scratch test to the castor bean meal dust, a wheal 1.5 cm. in diameter with pseudopodia and erythema developed and persisted for more than an hour. Since negative results were obtained with all the allergens except castor bean meal dust, intradermal tests were done with the same allergens, excluding castor bean meal dust. The results of the intradermal tests, except the one with the dust concentrate extract, were negative. With the dust extract, a wheal about 1 cm. in diameter with very little pseudopodia and practically no erythema occurred.

The patient continued to improve very slowly and was advised to take the antihistaminic drugs, bronchodilators, if necessary, and strictly to avoid any contact with castor bean products.

SUMMARY

A case of castor bean meal dust allergy has been presented, together with a review of the literature. The serious results from contact with this allergen have been stressed. Those whose occupation may expose them to this material, should be warned as to its dangers. Caution must be observed by allergists in testing for sensitivity to this potent allergen.

REFERENCES

1. Barnard, J. H.: J. Allergy, 1:473, 1930.
2. Bennett, R. H., and Schwartz, E.: J. Allergy, 5:427, 1934.
3. Bernton, H. S.: Am. J. M. Sc., 165:196, 1923.
4. Ehrlich, P.: Deutsch. Med. Wchnschr., 17:976, 1891. Cited from Sollmann, T.[9]
5. Feinberg, S. M.: Allergy in Practice. Year Book Publishers, 1946.
6. Figley, K., and Elrod, R. H.: J.A.M.A., 90:79, 1928.
7. Osborne, T. B.; Mendel, L. B., and Harris, I. F.: Am. J. Physiol., 14:259, 1907.
8. Ratner, B., and Gruehl, H. L.: Am. J. Hyg., 10:236, 1929.
9. Sollmann, T.: A Manual of Pharmacology. Philadelphia: W. B. Saunders Company, 1936.
10. Stillmark: Inaugural Dissertation Dorpat, 1888. Cited from Sollmann, T.[9]

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12. Randolph, T. G.; Rollins, J. P., and Walter, C. K.: Allergic reactions following the intravenous injection of corn sugar (dextrose or glucose). In press: Arch. Surgery, 61:554, 1950.
13. Randolph, T. G., and Rollins, J. P.: Allergic reactions from the ingestion or intravenous injection of cane sugar (sucrose). J. Lab. & Clin. Med., 36:242, 1950.
14. Randolph, T. G., and Rollins, J. P.: Beet sensitivity: Allergic reactions from the ingestion of beet sugar (sucrose) and monosodium glutamate of beet origin. J. Lab. & Clin. Med. Accepted for publication.
15. Rinkel, H. J.: Food allergy. II. The technique and clinical application of individual food tests. Ann. Allergy, 2:504, 1944.
16. Rinkel, H. J.: Food allergy. V. The function and clinical application of the rotary diversified diet. J. Pediat., 32:266, 1948.
17. Ruh, H. O., and Garvin, J. A.: Anthocyaninemia and anthocyaninuria. Ohio State M. J., 20:763, 1924.

MOLDS AS INHALANT ALLERGENS

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OUR interest in allergenic molds is reflected in a long chain of observations up the years from miasmatic effluvia to our present position where a tremendous literature on the mycologic aspects of antibiotic research affords us a sounder, more comprehensive background from which to expand our appreciation of the clinical problems presented by the mold allergies.

It will be recalled that prior to Van Leeuwen's observations[14,15,16] on the environmental aspects of mold spore exposure, little of a specific nature had been published to guide us in our interpretation of these mold spore responses. Through his efforts, Hansen,[11] Jiminez-Diaz and others[12,13] were stimulated to investigate allergic responses to a relatively small group of mold spores commonly encountered within the home.

This emphasis on the environmental pattern of mold spore exposure by the European School found its counterpart in a broader point of view as pioneered by Stakman,[25,26,29] Durham,[2,3,4,5] Bernstein and Feinberg,[1,6,7,8,9] Prince, Morrow et al,[17,18,19,20,21,22,23,24] Wittich[26,27,28,29] and Hansel.[10]

No doubt, emphasis in this country on the general nature of mold spore problems was influenced by our initial concentration on the widespread respiratory problems presented by atmospheric pollinosis, its logical parallel. Whatever may have been the logic or the need, the published data relating to spore-incidence curves across the country and throughout the seasons now enables us to evaluate seasonal sensitivity to the spores of Fungi imperfecti almost as clearly as we do those stemming from a specific response to the pollens of locally encountered trees, grasses and weeds.

Having provided ourselves with a workable program for handling the atmospheric type of mold problem, it appears fitting and proper to renew our interest by more fully evaluating those frequently overlooked environmental sources for mold spore development and circulation within the home itself. Before presenting a few clinical experiences encountered in evaluating inhalant mold patterns within the home, let us first look at an example of the usual atmospheric mold type of problem as we see it in the midwest.

A. K., a sixty-one-year-old woman, has annually had an incapacitating degree of seasonal asthma since childhood. Dissatisfied with attempts at ragweed hyposensitization elsewhere, she has, for some years, been spending the fall in California, where she has been more or less free of distress. The fact that symptoms in Wisconsin preceded actual ragweed pollination and persisted far beyond the pollination period of this particular allergenic weed raised the suspicion of atmospheric mold spores as possible offenders. Positive delayed skin tests to and properly graduated hyposensitizing doses of Fungi imperfecti enabled this patient to remain in Wisconsin with very

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minimal symptoms throughout the fall following six months of allergic management. This is the sort of person for whom windy days in the autumn and open bedroom windows at dawn are anathema.

An interesting observation among children has been the occurrence of severe episodes of bronchial asthma following raking up and romping about in leaves during October when mold-spore counts in this locality reach a peak. We have encountered a number of mold-sensitive children in whom this suggestive lead was confirmed by skin testing and clinical improvement resulting from hyposensitization to mold spores of Fungi imperfecti.

There appear to be, however, more subtle aspects of the problem—features of an environmental nature, of significance in those patients failing to experience perennial relief with so simple an analysis as the foregoing. Attempts to analyze the environmental allergenic pattern frequently bring one face to face with some interesting features relating to the inadvertent cultivation and circulation of allergenic spores within the home.

R. T., the seven-year-old son of a returning veteran, developed bronchial asthma within a few days after his father removed household furnishings from six years of wartime storage and resettled the family in its present home. Since the asthma was almost exclusively related to the child's sleeping habits, the bedroom was held under suspicion. The usual items such as feather pillows, dust-retainers and the rest which generally make up the offending allergenic moiety were ruled out by skin test and trial but when the boy's mattress, from which we obtained *Aspergillus ochraceus* in pure culture, was enclosed in an allergen-proof mattress cover he quickly began to improve.

Incidentally, a deliberate study of several hundred cotton mattresses discloses that, from more than one-third, one is able to obtain a pure culture of *Rhizopus nigricans.** A later report on reagins by the Prausnitz-Kustner technique to these as well as other specific mold spore responses will be presented.

C. H., a forty-five-year-old woman, was seen for a perennial nasal allergy, unsuccessfully treated by an assortment of nasal medications. Prompt withdrawal of all nose drops left the nose blocked and without the evanescent relief afforded by their decongestive action. In our allergic studies, we cultured *Rhizopus nigricans* from her mattress, whereupon, against advice, she discarded it and purchased a new one from a local department store. This, in turn, yielded a pure culture of *Mucor sp.*, so finally an allergen-proof mattress cover was procured and relief obtained. Hyposensitization to combined molds and dust has enabled her to remain asymptomatic for months.

C. K., a forty-three-year-old asthmatic patient, as well as I. K., his twenty-one-year-old son (a nasal allergic), experienced increased symptoms after establishing a "beer depot," on the second floor of which he now maintains his residence. A mold-survey (4/9/48) on Sabouraud petri plates revealed a heavy and diversified growth

*Subsequent cultures from bales of cotton as received by a local mattress manufacturer show *Rhizopus nigricans* when samples were taken from the center of the bales. Could this mold be regionally responsible for allergic symptoms in the South where this material originates?

of molds. This patient was hyposensitized to mold spores and his entire establishment fumigated with formaldehyde vapor. In keeping with modern refrigeration procedure, we suggested that he install sterilizing tubular lamps in the area. This was done, and both individuals have, aside from an occasional mild inconvenience, been much more comfortable than heretofore. A subsequently exposed petri plate (7/14/48) revealed a very marked diminution in circulating spores.

M. S., a thirty-three-year-old mother, and her three allergic daughters, ranging from three to ten years of age, had been having severe naso-bronchial symptoms. When first seen, their discomfort, at first seasonal, finally had become perennial, so environmental studies were carried out. Their home, heated by a hot-air type unit, was liberally furnished with mold spores emanating from a damp basement, which contained among other things a mold-laden incinerator. When this was removed, the home fumigated, sterilizing tubular lamps installed, and hyposensitization to mold spores carried out, a very satisfying improvement was noted in all. Within the past month the mother, going into the attic for the annual spring cleaning, was seized with a severe attack of the original symptoms. Investigation revealed a leaky roof with a resulting permeation of the attic contents by molds over-running the mildewed area.

V. K., a thirty-year-old woman, was referred by her otorhinolaryngologist consultant because of repeated polyp formation. When mold spores were found to feature prominently in her allergic pattern, we discovered a major hazard in her husband's enthusiastic hobby of raising rare tropical fish. It appears that the fertility of these fish is dependent upon a diet which includes special grubs raised in moldy bread and soil. Large pans of this mildewed material in the basement provided a constant source of spores, which were actively circulating throughout the house by way of the hot-air heating unit. The husband, with rare good humor and understanding, abandoned his cherished hobby and fumigated the home. His wife's progress from this point on, with proper hyposensitization to mold spores, has well rewarded his sacrifice.

These and similar experiences with musty kapok-filled toys, a baby wrapped in a mildewed blanket during a snow storm, a boy's enthusiastic salvaging of an older brother's mildewed jacket and parka, long ignored on a pile of castaways in the basement, and the exaggerated allergic symptoms accompanying wash day in the basement—these and many others emphasize how mold-supporting peculiarities of the patient's own environment may influence his allergic responses and remind us of the need for environmental mold surveys in an effort to eliminate, as well as to hyposensitize, to molds as inhalant allergens.

REFERENCES

1. Bernstein, T. B., and Feinberg, S. M.: Air-borne fungus spores: a five-year survey of daily mold spore content of Chicago air. J. Allergy, 13:231, 1942.
2. Duke, W. W., and Durham, O. C.: Pollen content of the air. J.A.M.A., 90: 1529, 1928.
3. Durham, O. C.: Incidence of air-borne fungus spores. I. Alternaria. J. Allergy, 8:480, 1937.
4. Durham, O. C.: Incidence of air-borne fungus spores. II. Hormodendrum, Alternaria and rust spores. J. Allergy, 10:40, 1938.
5. Durham, O. C.: Atmospheric allergens in Alaska. J. Allergy, 12:307, 1941.
6. Feinberg, S. M.: Mold allergy; its importance in asthma and hay fever. Wisconsin M. J., 32:254, 1935.

7. Feinberg, S. M., and Little, H. T.: Studies on the relation of microrganisms to allergy. III. A year's survey of daily mold spore content of the air. J. Allergy, 7:149, 1936.
8. Feinberg, S. M.: Seasonal hay fever and asthma due to molds. J.A.M.A., 107: 1861, 1936.
9. Feinberg, S. M.: Asthma and allergic rhinitis from molds: an analysis of 90 cases. Journal-Lancet, 57:87, 1937.
10. Hansel, F. K.: Hay fever, the value of daily atmospheric counts of pollen grains and mold spores in diagnosis and treatment. J. Missouri M. A., 37:241, 1940.
11. Hansen, K.: On mold asthma. Verhandl. d. deutsch. Gesellsch. f. inn. Med., 40:204, 1928.
12. Jiminez-Diaz, C.; Sanchez-Cuenca, B., and Parra, J.: Relation of asthma to abode of patient. Arch. d. med., cir. y especialid., 34:284, 1931.
13. Jiminez-Diaz, C.; Sanchez-Cuenca, B., and Puig, J.: Climatic asthmas. J. Allergy, 3:396, 1932.
14. Leeuwen, W. S., van: Bronchial asthma in relation to climate. Proc. Roy. Soc. Med., 17:19, 1924.
15. Leeuwen, W. S., van: Allergic disease in relation to climate (allergen-proof chamber). Internat. Clin., 2:1, 1927.
16. Leeuwen, W. S., van; Bien, Z.; Kremer, W., and Varekamp, H.: On the significance of small spored types of aspergilli (type of Aspergillus fumigatus) in the etiology of bronchial asthma. Ztschr. f. Immunitätsforsch. u. exper. Therap., 44:1, 1925.
17. Morrow, M. B.; Lowe, E. P., and Prince, H. E.: Mold fungi in the etiology of respiratory allergic diseases. I. A survey of air-borne molds. J. Allergy, 13:215, 1942.
18. Morrow, M. B., and Lowe, E. P.: Molds in relation to asthma and vasomotor rhinitis. Mycologia, 35:638, 1943.
19. Morrow, M. B.: Mold fungi in the etiology of respiratory allergic diseases. VII. Further survey studies. Ann. Allergy, 5:442, 1947.
20. Prince, H. E.; Selle, W. A., and Morrow, M. B.: Molds in the etiology of asthma and hay fever: a preliminary report. Texas State J. Med., 30:340, 1934.
21. Prince, H. E., and Morrow, M. B.: Molds in the etiology of asthma and hay fever with special reference to the coastal areas of Texas. South M. J., 30:754, 1937.
22. Prince, H. E., and Morrow, M. B.: Air-borne molds in the etiology of respiratory allergic diseases. Tri-State M. J., 11:2277, 1939.
23. Prince, H. E., and Morrow, M. B.: Mold fungi in the etiology of respiratory allergy: a survey of air-borne molds. Proc. Int. Cong. Microbiol., 270-271, 1939.
24. Prince, H. E.: Non-pollen factors simulating seasonal respiratory allergy. South. M. J., 32:956, 1939.
25. Stakman, Elvin C.: Spores in the upper air. J. Agr. Research, 24:599, 1923.
26. Wittich, F. W., and Stakman, E. C.: Case of respiratory allergy due to inhalation of grain smuts. J. Allergy, 8:189, 1937.
27. Wittich, F. W.: Further observations on allergy to smut. Journal-Lancet, 59:382, 1939.
28. Wittich, F. W.: The nature of various mill dust allergens. Journal-Lancet, 60:418, 1940.
29. Wittich, F. W., and Stakman, E. C.: Case of respiratory allergy due to inhalation of grain smuts. J. Allergy, 8:189, 1937.

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Progress in Allergy

ALLERGY TO VIRAL AND RICKETTSIAL VACCINES
Review of the Literature

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THE propagation of chicken sarcoma on chorioallantoic membrane of the chick embryo[40] led Goodpasture and his co-workers to develop this medium for the culture of fowl-pox and vaccinia viruses.[22,54] Soon the technique proved successful for the growth of other viruses, among them, the virus of herpes simplex,[46] Newcastle disease[7] and western equine encephalomyelitis. The latter proved useful in the preparation of a vaccine in sufficient quantity to be applied to the immunization of domestic animals and of man.[2] Reports on rickettsiae successfully grown on the chorioallantoic membrane appeared in 1934.[34,55] Bengtson and Dyer[3] worked with Rocky Mountain spotted fever in 1935, but it remained for Cox[11] to develop a method which made available rickettsial vaccines for large scale production, which soon found application in the armed services. Another technique utilizing the entire chick embryo was presented in the preparation of yellow fever virus vaccines.[50] Allantoic fluid culture of influenza virus was developed by Burnet[6] in 1941. In this way, it has become possible to provide a ready source of viruses and rickettsiae for clinical trial. Thus far, the vaccines which may be considered of value as immunizing agents are those against yellow fever, typhus fever, Rocky Mountain spotted fever (tick typhus), Influenza Virus A and B infections, and mumps. There is no doubt that the search for and development of vaccines against other viral and rickettsial diseases will continue. The fact that these disease-producing agents display a great avidity for growing on embryonal tissues of the fertilized egg has brought into sharp relief the possibility of allergic reactivity that must inevitably ensue with so potent an antigen as egg protein.

ALLERGIC REACTIVITY OF CHICK EMBRYO VACCINES IN ANIMALS

The early use of equine encephalomyelitis vaccine (E.E.V.) in domestic animals made it evident that allergic reactivity could result. Schoening[41] reported local and systemic reactions in horses when reinjected with E.E.V. Anaphylactic shock in some instances terminated fatally. Similar observations were made by Graham.[24] Wolfe and Trum[53] described anaphylactic shock followed by typical desensitization in the recovery period. Putting these observations to the test of the laboratory animal, van der Scheer et al[51] showed that guinea pigs can be sensitized with E.E.V. and fatally shocked on receiving a second inoculation. Berge and Hargett[4] ascribed the reactions following E.E.V. to antigens which developed in the older embryo, and which were more active than those of the younger embryo. As a result of guinea pig anaphylaxis experiments, they concluded that typhus vaccine, Rocky Mountain spotted fever vaccine and American "Q" fever vaccine derived from yolk sac of embryos less than ten days of age should prove even less antigenic. Subsequent reports have not supported these contentions as will be shown in the review of clinical experiences which indicate that cultures from younger embryos are highly antigenic. Some indication of the nature of the antigens contained in these vaccines is offered by Cohen,[9] Knight,[27,28] Coulson and Stevens,[10] and Engel and Randall.[15]

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The predilection of rickettsiae and viruses for specific embryo structures influences the type of egg antigen dominant in the vaccine. The rickettsiae of typhus and "Q" fever thrive best in yolk sac fluid and membrane; of Rocky Mountain spotted fever in yolk sac and chorioallantoic membranes; the virus of influenza, in the amniotic and allantoic fluid, while equine encephalomyelitis and yellow fever viruses thrive best on embryonal tissue, itself. The allergic reactions which ensue may result from such antigenic specificities. An individual predominantly sensitive to egg white might conceivably react to influenza vaccines, as has been emphasized by Ratner and Untracht,[36] and one predominantly sensitive to egg yolk would react more markedly to typhus vaccine and less to yellow fever vaccine as has been demonstrated by Rubin.[42] Another individual, presumably sensitive to egg white and egg yolk, reacted successively to typhus and to influenza vaccine, given a year apart.[41] Experimental support for this capacity for specific reaction is offered by Coulson and Stevens who found that, although egg yolk and egg white have antigens common to both, they also have antigens independent of each other. Some studies indicate that chick embryo and embryonic fluids are more highly antigenic and that vaccines grown on membrane have a reduced anaphylactogenicity. Coulson and Stevens indicated that suspensions of washed rickettsial bodies derived from yolk sac culture contain egg antigens in quantities which are close to the minimum sensitizing dose, while Cox[12] failed to induce sensitivity with Rocky Mountain spotted fever and typhus vaccines derived from membrane inoculated cultures.

ALLERGIC REACTIVITY OF CHICK EMBRYO VACCINES IN THE HUMAN

The experiences with animal immunization have been closely borne out in the use of these vaccines in human beings who have displayed the whole gamut of allergic reactivity.

In the nonsensitive individual, the earliest form of allergic manifestation, namely, a serum sickness-like reaction was described by Sulzberger and Asher[48] from primary yellow fever vaccine injection. Symptoms were pain in the joints, headache, fever, nausea and vomiting, with a rash of the urticarial and erythema multiforme types. These appeared six and seven days after the injection, respectively, in two individuals. In a third, the symptoms were similar in appearance, but were manifested earlier, following thirty-six hours after the injection, thus indicating a shortened incubation period.

Local serum sickness-like urticarial rash and induration at the site of injection were noted by Stull[47] in a thirty-three-year-old man, seven days after injection of 1 cc of E.E.V. That this vaccine may potentiate hypersensitivity was indicated when on reinjection of the same dose two weeks later, a large local reaction appeared within one hour and lasted for six days. A similar episode was described by Lieder[29] on second injection of equine encephalomyelitis vaccine. Beard, Finkelstein and Beard,[1] too, have noted more severe effects at the site of reinjected E.E.V. In nine persons who were revaccinated, they observed symptoms of "crampy stiffness" and muscular soreness at the injected area. It is not entirely clear that these reactions are allergic since the dose given was large, and its absorption slow, in view of its heavy protein content, as pointed out by Coulson and Stevens. However, that the vaccine may sensitize and shock horses and guinea pigs has been indicated above.[4,24,44,51,53] Similar acceleration in the appearance of the local reaction at the site of injection was described by Beveridge and Burnet[5] after repeated intradermal injection of influenza virus vaccine.

For the most part, the reactions reported occurred in individuals who were spontaneously sensitive to egg proteins. Severe anaphylactic shock reactions have followed injections of yellow fever, typhus and influenza virus vaccines in egg-sensitive persons. In 1943, Swartz[49] recorded the case of a profound anaphylactic reaction with blurred vision, labored breathing, nausea, vomiting, diarrhea, urticaria,

edema and unconsciousness following a single injection of yellow fever vaccine with cholera vaccine within five minutes after its administration. Skin reactions to egg and chicken proteins were demonstrated as were circulating allergic antibodies. Sprague and Barnard[46] described similar alarming reactions from yellow fever and typhus inoculations. With typhus vaccine, there have been eight instances of such severe anaphylactic reactions; two additional instances resulted from influenza virus vaccine. Park[34] reported a reaction to the egg allergen in typhus vaccine. A British airman, aged thirty-five, was admitted in collapse, vomiting blood and presenting asthmatic breathing and generalized urticaria. He soon became comatose. With symptomatic treatment, he recovered completely by the next morning when he related that he had received an injection of typhus vaccine fifteen minutes before the described reaction occurred. He revealed that he had been allergic to egg all his life. His usual reaction to egg was vomiting or, if it did not occur, edema of the lips, tongue and larynx. Asthma and urticaria would follow. Never before had he vomited blood or passed into coma. Skin tests were positive to egg proteins by the scratch method and also with passive transfer tests. Park reported that his patient had received an inoculation of yellow fever vaccine about a year previously without any ill effects. Apparently he was sensitive to the yolk allergen.

Another typical case is that reported by Roth[39] in a soldier, aged nineteen. Immediately after the first injection of typhus, the patient had extreme dyspnea, cough, weakness and substernal pressure. He had a temperature of 97.4°F., a pulse rate of 128, and a weak respiratory rate of 24. His skin was cyanotic and covered with an urticarial eruption; his face was edematous; his lungs were filled with asthmatic rales. The patient recovered in four days. Three days later, he was given 0.1 cc of typhus vaccine, and a severe asthmatic attack followed immediately; but he did not have shock or cyanosis as before. He presented asthmatic rales, a temperature of 98.6°F., a pulse rate of 120, and a respiratory rate of 36. Recovery ensued in thirty-six hours. It is of interest that when he was profoundly affected, his respiratory rate was only 24, and later when his reaction was milder, his respiratory rate was 36. This is an important criterion for the severity of an attack; the slower the respiratory rate, the greater the danger of asphyxial death.

Other reports of severe systemic reactions with shock, asthma, urticaria, nausea and vomiting in some instances, have been recorded by Sprague and Barnard,[46] Hampton,[26] Lieder, [29] Plotz[35] and Rubin.[41] In the case reported by Plotz, the patient suffered a severe reaction from the test dose when she was tested intracutaneously with typhus vaccine following her recovery from the shock reaction. Further vaccination procedure was therefore withheld. Rubin's case had a recurrence of severe shock one year following the typhus injection when he received 1 cc of influenza vaccine. Within five minutes he developed asthma and generalized urticaria, which gradually subsided in four days. An interesting anaphylactic reaction was reported in a twenty-five-year-old member of the Women's Army Corps.[36] She developed a markedly lowered blood pressure about thirteen hours after an injection of 1 cc of influenza vaccine. There was no wheezing or urticaria, the cardinal symptom being a fall in systemic blood pressure. It is probable that this woman suffered a canine type of anaphylactic reaction. She revealed a history of life-long egg intolerance.

Evidence for the dependence of these reactions upon chick embryo and egg sensitivity was obtained from a history of pre-existing intolerance for foods containing these proteins in almost every instance. Swartz, Park and Hampton succeeded in proving the antigenic identity of typhus vaccine with egg proteins by means of skin tests and passive transfers.

Moderately severe systemic allergic reactions have also been described following the administration of typhus, yellow fever and influenza virus vaccines. In these instances, urticaria, angioneurotic edema, gastrointestinal disturbances, milder

asthmatic episodes without shock symptoms were the syndromes which followed prophylactic or diagnostic inoculation. Roth[39] mentions eight moderate allergic reactions after typhus injection, in addition to the severely shocked individual described above. In only four of this total of nine cases was a history of egg sensitivity known to the individuals concerned. Raynolds[37] described the case of a nurse who developed a blotchy rash of the face, neck and back fifteen minutes after an intradermal test dose of typhus vaccine. Interestingly enough, there was a negligible dermal response to this test injection. The patient revealed a history of having suffered urticarial rash of the face and neck after eating egg.

Rubin[42] described a soldier, aged nineteen, who developed edema of the eyes, urticaria of the cheeks and nose, and pain in the chest after an injection of typhus plus yellow fever vaccines. Skin tests on this individual are particularly interesting, since the dominant sensitivity appeared following egg yolk injection, while those to egg white and chicken meat were negligible. Direct test with yellow fever vaccine was two plus positive, while typhus vaccine was four plus. Passive transfer to egg yolk developed a three plus reaction. This individual could tolerate hard-boiled egg white, but vomited when whole egg was eaten. His sensitivity, apparently, depended greatly upon the yolk antigen, and bears out the contention of Coulson and Stevens that egg yolk and egg white may have antigenicity independent of each other.

Three reports are recorded concerning influenza virus vaccine reactions of a moderately severe nature. Eaton and Meiklejohn[15] described one case of moderately severe asthma in an individual who had had no history of allergy previously, and two cases of urticaria. Magill, Plummer, Smillie and Sugg[30] mention an instance of angioneurotic edema of the face and lips. Ratner and Untracht[36] reported the occurrence of asthma when a nine-year-old boy was tested with influenza vaccine. Another child, aged six years, developed generalized urticaria and asthma after injection of 0.5 cc. In both these instances, there was a history of intolerance for egg or egg-containing food.

The systemic allergic reactions described above are all instances in which the individuals recovered. The hazard of injection of these vaccines into exquisitely sensitive individuals revealed itself in six instances which proved fatal. Three fatalities followed typhus vaccine, one after a spotted fever vaccine, and two after influenza virus vaccine.

Rifkin[38] described the case of a soldier, aged twenty-four years, who died twenty-five minutes after injection of 1 cc of typhus vaccine. Autopsy in this case revealed a typical guinea pig type of anaphylactic lung. This individual had a history of nausea on ingestion of egg. Walker[52] described a sailor who was found dead in his bunk twenty-six minutes after having received his first injection of typhus vaccine. Within five minutes after injection he had complained of feeling ill, but had failed to seek aid. This individual had been obliged on occasion to seek relief from duty because of feeling ill after ingestion of egg. He had been sensitive to egg all his life. It is of interest that he had previously received an injection of yellow fever vaccine with no ill effect. It is not known whether this yellow fever vaccine was of the type cultured on egg embryo media. Autopsy of this case revealed a typical guinea pig anaphylactic lung with multiple hemorrhages.

Plotz[35] reported the death of a soldier who had received typhus and cholera vaccines thirty minutes previously. In this instance, too, autopsy revealed typical guinea pig anaphylactic lungs. In the same report, Plotz described the death of a soldier two hours after injection of influenza virus vaccine. This individual had had a history of asthma since childhood. An additional death in this report was that of a child who had received a spotted fever vaccine. The death in this instance was reputed to be typical of anaphylaxis. This case is quoted from the Department

of Health record in Washington, D. C., and may be the same as the case referred to by Forman.[20]

More recently, Curphey[13] reported a case of a three-and-a-half-year-old child who received a subcutaneous injection of 0.5 cc of influenza A and B vaccine. The family physician at the same time administered a similar amount of vaccine to two other sisters, five and eight years, respectively, and also to the mother and grandmother, who received 1 cc each. All the injected individuals had little or no reaction, except the three-and-a-half-year-old, who complained of pains in the abdomen, chills, followed by vomiting and convulsions which developed four hours after the injection of the vaccine. At this time, examination of the child showed a rectal temperature of 109°F.

History revealed no evidence of allergy. On admission to the hospital within two hours after the onset of symptoms, the patient was cyanotic with widely dilated pupils. Moist rales were heard in both pulmonary fields; the heart rate was 180 per minute. The extremities showed convulsive contractions during examinations. Epinephrin and oxygen did not relieve the symptoms. The bleeding time was prolonged, and, moreover, bleeding points appeared wherever a needle was inserted. The temperature fell to 103°F. The heart rate increased in rapidity up to 240 per minute, but remained regular. Cheyne-Stokes respirations ensued. Convulsions occurred every two minutes. Two hours after entry into the hospital, breathing ceased, and after artificial respirations were instituted, the rhythm resumed, but with constant bilateral twitchings and spasms. Seven hours after the onset of symptoms, the child collapsed completely; her condition deteriorated until she died in coma.

Necropsy findings in this case were not characteristic of anaphylaxis—neither the pulmonary type seen in the guinea pig nor the canine type affecting the liver. Curphey regarded it as a hemorrhagic form of anaphylaxis. He considered the hemorrhages as having resulted from a Shwartzman-phenomenon-like reaction. He noted that, on autopsy, an early pneumonia was evident which possibly was due to a virus infection. He reasoned, therefore, that this virus had sensitized the child to such a degree that the prophylactic injection of influenza virus vaccine precipitated a necrotic type of remote response similar to that seen in the Shwartzman reaction in the rabbit. From the fact that this child was not shown to be sensitive to egg and did not show typical anaphylaxis and had a temperature of 109°, which is not consonant with the picture of anaphylaxis, it must be assumed that the child died as a result of the injection, but not necessarily from anaphylaxis.

Salk[18] raises the interesting question, as does Curphey, that perhaps the virus, itself, was responsible for the death.

If Curphey's case was a toxic reaction to some "foreign protein," as he suggested in his comment, then the question raised by Salk is of considerable importance. Salk believes that the primary toxic reactions to the virus vaccines are proportional in frequency and severity to the concentration of virus injected. The more severe reactions that were observed in adults, given rather large doses of virus concentrated and purified by differential centrifugalization, frequently began four to five hours after injection, a time of onset similar to that in the case described by Curphey. The symptoms and signs of reaction were chills, fever up to 103°F. recorded orally, severe headaches, vomiting, agitation and anxiety, body aches, and varying degrees of prostration. In a few cases, in these experimental studies with large doses, the reactions were somewhat alarming. In a limited experience with young infants and children, Salk found reactions of greater severity, accompanied by higher temperatures than with adults.

To sum up, then, we are confronted with differentiating the true allergic reactions from the nonallergic, or "primary toxic" reactions. The former are: (1) sudden and explosive, (2) with no hyperpyrexia, (3) manifested as dermal, respiratory and anaphylactic shock reactions and, (4) occur in individuals in whom a history of

egg allergy or the presence of positive skin reactions to the allergen can be elicited. The latter are: (1) delayed in onset, (2) with varying degrees of hyperpyrexia, (3) presenting none of the manifestations of classical allergic reactions and, (4) occur in individuals who do not have a history of allergy to egg or positive allergic skin reactions.

When a patient dies in shock, several of the criteria of anaphylaxis must be present at necropsy, in order to diagnose the condition as allergic. A careful evaluation of the tenets of an allergic, as differentiated from a nonallergic individual, must be made in the final analysis of a case.

The history of allergy to egg is very valuable in appraising hypersensitivity, but is not always so reliable a criterion as one would expect. Swartz,[40] for example, in his case obtained the interesting data that, at four years of age, his patient of twenty-seven had been fed large quantities of egg and egg-white during an illness. From that time on, he was unable to eat eggs. He not only had an aversion to them, but the ingestion of the smallest amount of egg-containing food precipitated severe asthmatic paroxysms. He also was hypersensitive to other foods, as well as to feathers. On the other hand, Roth,[39] who reported on nine cases of allergic reactions to typhus vaccine obtained a history of allergy to egg in only four. Further, we studied 108 allergic children[36] of whom only eleven were found sensitive to egg; in two of these, an allergic systemic reaction ensued from the injection of influenza vaccine. Of these two cases, one gave a history of sensitivity to egg from infancy, and the other was not cognizant of his egg sensitivity until it was determined by us three years previously. It was evident from our eleven cases, too, that despite a real history of egg sensitivity the majority did not suffer systemic reactions. Only 50 per cent of them were sufficiently sensitive to egg white to be regarded sensitive to a degree high enough to warrant fear in administering the vaccine.

The striking fact gleaned from our study was that of 108 truly allergic children who were all carefully studied and under observation for one to several years, allergy *per se* was not the dominant factor. Sensitivities other than to egg did not influence the reaction to influenza vaccine at all. Moreover, only two out of the 108 children, or approximately 2 per cent, were truly markedly sensitive to egg white. Therefore, whereas in our paper we regarded 4.6 per cent who had definite marked dermal reaction to egg white as comprising the potential hazards, we now believe that this figure should be reduced to less than 2 per cent. In our paper, we stated, "If the incidence of allergy in the general population is 10 per cent, then the serious egg allergenicity in the general population would be 5 per cent of 10 per cent, or 0.5 per cent, or one in every 200 persons." Corrected as indicated, therefore, the figure should be less than 2 per cent of 10 per cent, that is one, or perhaps two in every 1,000 persons.

If sensitivity to egg is more prevalent among children, as are all food sensitivities, then this figure can be considerably reduced for the general population. If comparable figures are obtained with adults, the exact number for the general population should be small indeed. This is in accord with the point of view of Plotz, and is borne out by the experience in the army, quoted from Hampton.[26] A total of 8,419 military personnel were injected at one post between August, 1944 and August, 1945 with typhus vaccine, and only one anaphylactic reaction occurred in this group.

If one in 8,000 or 9,000 adults reacted severely to 1 cc of typhus, then with further purification of the vaccines and small intracutaneous doses of 0.1 cc, the dangers of anaphylactic shock or death will be reduced to the extremely low figure of one in many thousands.

Still another interesting phase of this problem remains for the future—and that is the danger inherent in developing an acquired sensitivity to egg proteins from repeated injections of this type of vaccine.

The late Dr. Plotz made a real attempt to study this phase.[35] Of a group of 150 individuals who were not sensitive to egg and who were vaccinated with three weekly subcutaneous 1 cc injections of typhus vaccine, nine of the 150 vaccinated subjects developed cutaneous sensitivity. In all nine cases, cutaneous sensitivity was noted four weeks after the third dose; one to egg yolk and egg white; four to vaccine, alone; two to vaccine and egg yolk, and two to vaccine, egg yolk and egg white. The cutaneous sensitivity became negative after twelve weeks in seven of the cases, and diminished considerably in two. In these two persons, the cutaneous reactions remained relatively unchanged twelve weeks after the third dose. These two subjects must have been sensitized to a greater degree than the others—they reacted to egg yolk, egg white, and vaccine. Despite the cutaneous sensitivity, all the subjects sustained a subsequent subcutaneous injection of the full dose of typhus vaccine without systemic reaction.

In a study of about 322 children, which is to be published, we noted that no marked cutaneous sensitivity to egg resulted from influenza A and B vaccine administered in 0.1 cc intradermal doses. Similar results are reported by Gold and Hampil with repeated equine encephalomyelitis vaccine injections.[21]

On the other hand, we must conjure with the case of Stull[47] who relates that in a patient, aged thirty-three, a delayed allergic urticarial local reaction occurred seven days after the first injection of 1 cc of equine encephalomyelitis vaccine (local serum sickness-type reaction). Two weeks later, a second injection of 1 cc produced a large local reaction within one hour (accelerated reaction indicating allergy) which lasted for six days. Since that time, this patient has had gastrointestinal disturbances with severe diarrhea following the eating of chicken or eggs. The serum of this recipient contained antibodies to egg yolk and chicken embryo, but not to egg white.

It would be interesting to know how long such clinical allergy persists. In the light of this case, one must recognize that despite the paucity of such occurrences, children and adults may become systemically sensitized to egg protein if the vaccines are used extensively. Here, too, in the reduction of this hazard, much will depend upon the smallness of the dosage and the refinement of vaccines. It must further be remembered that the equine encephalomyelitis vaccine used in this case is about twenty times more antigenic than other vaccines of this group.

Another interesting phase of allergy to virus vaccines cultured from egg embryo is the cutaneous reactivity of a delayed or tuberculin type which follows intradermal injection and results from sensitivity to the virus protein. This dermal sensitivity acquired from natural infection with the viruses and also from prophylactic vaccination is therefore reputed to be useful in indicating the immunologic status of the individual. A negative reaction to a test dose would thus be indicative of susceptibility to infection, whereas a positive response, indicating previous experience with the virus, would point to a state of immunity. With regard to mumps, usefulness of this type of dermal test is at present undergoing clinical evaluation.[8,16,17,19,28,32] Antigen for the Frei test for lymphogranuloma venereum may be derived from egg embryo culture.[23] Other virus infections which may induce delayed allergic reactivity to virus protein include influenza,[5] herpes simplex[33] and meningopneumonitis in rabbits.[31]

In conclusion, we should like to state that, whether the individual is highly allergic to egg yolk or egg white the hazard can be minimized if the suggestion made by Ratner and Untracht[36] is followed. All persons should be tested intradermally with undiluted vaccine, using 0.02 cc, before administering each and every prophylactic dose to establish whether a person is negative to the egg protein, moderately sensitive, or markedly so. The vaccine should be withheld if the reaction is a systemic or a severe local one. All the studies point to this single criterion as being of value.

BIBLIOGRAPHY

1. Beard, D. W., Finkelstein, H. and Beard, J. W.: Repeated vaccination of man against virus of equine encephalomyelitis. J. Immunol., 40:497, 1941.
2. Beard, J. W., Finkelstein, H., Sealy, W. C. and Wyckoff, R. W. G.: Immunization against equine encephalomyelitis with chick embyro vaccines. Science, 87:490, 1938.
3. Bengtson, I. A. and Dyer, R. E.: Cultivation of virus of Rocky Mountain spotted fever in developing chick embyro. Pub. Health Rep., 50:1489, 1935.
4. Berge, T. O. and Hargett, M. V.: Anaphylaxis in guinea pigs following sensitization with chick embryo yellow fever vaccine and normal chick embryos. Pub. Health Rep., 57:652, 1942.
5. Beveridge, W. I. B. and Burnet, F. M.: A cutaneous reaction to the influenza viruses. M. J. Australia, 1:85, 1944.
6. Burnet, F. M.: Growth of influenza virus in the allantoic cavity of the chick embryo. Australian J. Exper. Biol. & M. Sc., 19:291, 1941.
7. Burnet, F. M. and Ferry, J. D.: Differentiation of viruses of fowl plague and Newcastle disease: Experiments using technique of chorioallantoic membrane inoculation of developing egg. Brit. J. Exper. Path., 15:56, 1934.
8. Cabasso, V., Ruegsegger, J. M., Looser, G. K., and Cox, H. R.: The immunologic response of children to the injection of chick embryo-propagated mumps virus vaccine, as measured by the complement-fixation test. J. Lab. & Clin. Med., 35:771, 1950.
9. Cohen, S. S.: Cytoplasmic particles of chorioallantoic membrane and their relations to purified preparations of influenza virus. Proc. Soc. Exper. Biol. & Med., 57:358, 1944.
10. Coulson, E. J. and Stevens, H.: II. Anaphylactogenic properties of typhus fever and equine encephalomyelitis vaccine. J. Immunol., 53:321, 1946.
11. Cox, H. R.: Use of yolk sac of developing chick embryo as medium for growing rickettsiae of Rock Mountain spotted fever and typhus groups. Pub. Health Rep., 53:2241, 1938.
12. Cox, H. R.: Cultivation of rickettsiae of the Rocky Mountain spotted fever, typhus and Q fever groups in the embryonic tissues of developing chicks. (Theobald Smith Award Lecture). Science, 94:399, 1941.
13. Curphey, T. J.: Fatal allergic reaction due to influenza vaccine. J.A.M.A., 133:1062, 1947.
14. da Cunha, A. M.: Sur la culture des rickettsia du typhus exanthématique de São Paulo dans la membrane chorioallantoïde de l'Embryon de poulet. Compt. Rend. Soc. de Biol., 117:392, 1934.
15. Eaton, M. D. and Meiklejohn, G.: Vaccination against influenza: A study in California during the epidemic of 1943-44. Am. J. Hyg., 42:28, 1945.
16. Enders, J. F., Cohen, S. and Kane, L. W.: Immunity in mumps. II. The development of complement-fixing antibody and dermal hypersensitivity in human beings following mumps. J. Exper. Med., 81:119, 1945.
17. Enders, J. F., Kane, L. W., Maris, E. P., and Stokes, J., Jr.: Immunity in mumps. V. Correlation of presence of dermal hypersensitivity and resistance to mumps. J. Exper. Med., 84:341, 1946.
18. Engel, L. L. and Randall, R.: Quantitative estimation of egg and chicken proteins in equine encephalomyelitis vaccine. J. Immunol., 55:325, 1947.
19. Florman, A. L., Fischer, A. F. and Moloshok, R. E.: Evaluation of the mumps skin test. Pediatrics, 5:469, 1950.
20. Forman, J.: Letter, Internat. Corr. Club. Allergy. Series 8:83, 1945.
21. Gold, H. and Hampil, B.: Results of skin tests following immunization against encephalomyelitis (Eastern and Western types) with bivalent vaccines of chick embryo origin. J. Allergy, 12:138, 1941.
22. Goodpasture, E. W., Woodruff, A. M. and Buddingh, G. J.: Vaccinal infection of chorioallantoic membrane of chick embryo. Am. J. Path., 8:271, 1932.
23. Grace, A. W., Rake, G. and Shafer, M. F.: A new material (Lygranum) for performance of the Frei test for lymphogranuloma venereum. Proc. Soc. Exper. Biol. & Med., 45:259, 1940.
24. Graham, R.: Reactions in horses following inoculation of chick embryo vaccine. J. Am. Vet. M. A., 97:38, 1940.
25. Habel, K.: Cultivation of mumps virus in the developing chick embryo and its application to studies of immunity to mumps in man. Pub. Health Rep., 60:201, 1945.
26. Hampton, S.: Anaphylactic shock in egg-sensitive individuals with typhus vaccine. J. Lab. & Clin. Med., 32:109, 1947.
27. Knight, C. A.: Precipitin reactions of highly purified influenza viruses and related materials. J. Exper. Med., 83:281, 1946.
28. Knight, C. A.: Nucleic acid and carbohydrate of influenza virus. J. Exper. Med., 85:99, 1947.
29. Lieder, L. E.: Letter. Internat. Corr. Club Allergy, Series, 8:58, 1945.
30. Magill, T. P., Plummer, N., Smillie, W. G. and Sugg, J. Y.: Evaluation of vaccination against influenza. Am. J. Hyg., 42:94, 1945.
31. Morgan, H. R.: Use of yolk sac antigens for skin tests in rabbits infected with the virus of meningopneumonitis. J. Immunol., 54:103, 1946.
32. Muntz, H. H., Powell, H. M. and Culbertson, C. G.: I. Mumps vaccine. J. Lab. & Clin. Med., 34:199, 1949.
33. Nagler, F. P. O.: A herpes skin test reagent from amniotic fluid. Australian J. Exper. Biol. & M. Sc., 24:103, 1946.
34. Park, R. G.: Allergy to egg-prepared vaccines. Brit. M. J., 2:570, 1945.
35. Plotz, H.: I. Skin sensitivity following the subcutaneous inoculation of typhus vaccines in humans. J. Immunol., 53:315, 1946.
36. Ratner, B. and Untracht, S.: Allergy to virus and rickettsial vaccines. I. Allergy to influenza A and B vaccine in children. J.A.M.A., 132:899, 1946.
37. Raynolds, A. H.: Correspondence, J.A.M.A., 128:613, 1945.
38. Rifkin, H.: Death due to administration of typhus vaccine. Ann. Int. Med., 25:346, 1946.
39. Roth, V. E.: Reactions to typhus vaccine. Bull. U. S. Army M. Dept., 88:111, 1945.
40. Rous, P. and Murphy, J. B.: Tumor implantations in the developing embryo: Experiments with a transmissible sarcoma of the fowl. J.A.M.A., 56:741, 1911.
41. Rubin, I.: Quoted by Ratner and Untracht.[36]
42. Rubin, S. S.: An allergic reaction following typhus fever vaccine and yellow fever vaccine due to egg yolk sensitivity. J. Allergy, 17:21, 1946.
43. Salk, J. E.: Reactions to influenza virus vaccines (Correspondence). J.A.M.A., 134:393, 1947.

44. Schoening, H. W.: Reactions following administration of equine encephalomyelitis vaccine. J. Am. Vet. M. A., 97:39, 1940.
45. Saddington, R. S.: Cultivation of herpes virus, and use of mouse in its titration. Proc. Soc. Exper. Biol. & Med., 29:1012, 1932.
46. Sprague, H. B. and Barnard, J. H.: Egg allergy: Significance in typhus and yellow fever immunization. U. S. Nav. M. Bull., 45:71, 1945.
47. Stull, C. A.: III. A study to determine whether chick egg yolk sac vaccines contained sufficient egg proteins to cause severe systemic reactions if given to egg-sensitive individuals. J. Immunol., 53:343, 1946.
48. Sulzberger, M. B. and Asher, C.: Urticarial and erythema multiforme-like eruptions following injections of yellow fever vaccine. U. S. Nav. M. Bull., 40:411, 1942.
49. Swartz, H. F.: Systemic allergic reaction induced by yellow fever vaccine. J. Lab. & Clin. Med., 28:1663, 1943.
50. Theiler, M. and Smith, H. H.: Use of yellow fever virus modified by *in vitro* cultivation for human immunization. J. Exper. Med., 65:787, 1937.
51. van der Scheer, J., Wyckoff, R. W. G. and Bohnel, E.: Antigenicity of chick embryo. J. Immunol., 41:391, 1941.
52. Walker, R. H.: Fatal anaphylaxis following typhus injection. U. S. Nav. M. Bull., 48:303, 1948.
53. Wolfe, W. R. and Trum, B. F.: Anaphylactic reactions following the use of chick embryo equine encephalomyelitis vaccine. Vet. Bull. U. S. Army, 34:226, 1940.
54. Woodruff, A. M. and Goodpasture, E. W.: Susceptibility of chorioallantoic membrane of chick embryos to infection with fowl-pox virus. Amer. J. Path., 7:209, 1931.
55. Zia, S.: Cultivation of Mexican and European typhus rickettsiae in chorioallantoic membrane of chick embryo. Am. J. Path., 10:211, 1934.

SHORTENING THE TREATMENT OF HAY FEVER

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more potent preseasonal injections. Of the sixty-five ragweed-sensitive patients receiving this technique, fifty-nine had an excellent result; five good; and one fair.

REFERENCES

1. Arbesman, C. E.; Koepf, G. F.; and Lenzner, A. R.: Clinical studies with n'Pyridil, N'Benzyl, Dimethylethylenediamine Monohydrochloride (Pyribenzamine). J. Allergy, 17:275-283, 1946.
2. Fuchs, A. M.; Schulman, P. M.; Strauss, M. B.: Clinical studies with Pyribenzamine (n'Pyridil-n'Benzyl-Dimethylethylenediamine) in hay fever. J. Allergy, 18:385-390, 1947.
3. Green, M. A.: Letters of the International Correspondence Society of Allergists, 10:100, 1947.
4. Maietta, A. L.: Unusually good results in pollinosis with combined antigen-antihistamine therapy. I. Shortening the treatment of hay fever. Ann. Allergy, 7:789, (Nov.-Dec.) 1949.

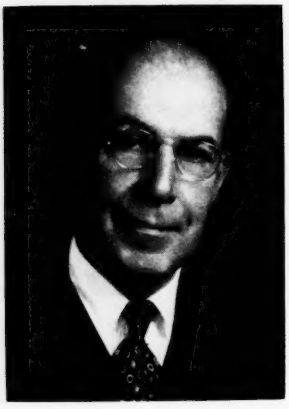
482 Beacon Street

Joseph R. Wiseman, M.D., F.A.C.A., and Richard D. Wiseman, M.D., announce their association in the practice of allergy and internal medicine. The address is Physicians Building, 608 East Genesee Street, Syracuse, New York.

Sol N. Keen, M.D., Associate Fellow of the College, announces the removal of his offices from 619 East Fifth Street to 311 East Seventeenth Street, New York 3, New York. Doctor Keen specializes in the practice of pediatrics and pediatric allergy.

IN MEMORIAM

WILLIAM F. PETERSEN, M.D., F.A.C.A. (Hon.)



Members of the College will grieve to learn of the sudden death of Dr. William F. Petersen. On August 7, while at work in his garden in Lake Geneva, Wisconsin, he was suddenly stricken with a cerebral hemorrhage; he was taken to Lakeland Hospital in Elkhorn, Wisconsin, and on August 14 was transferred to St. Luke's Hospital, Chicago, where he died August 20.

Doctor Petersen was born in Chicago, March 25, 1887, the son of Eduard Petersen, founder of the Petersen Oven Company. He attended the Armour Institute, and graduated from the University of Chicago in 1910 and from Rush Medical College in 1912. After doing graduate work in biochemistry and pathology at Harvard and Columbia Universities, he became Instructor and Assistant Professor of Experimental Medicine and Pathology at Vanderbilt University (1913-1917). During World War I he served in the Army Medical Corps. In 1919 he married Alma C. Schmidt, daughter of Dr. Otto L. Schmidt of Chicago, physician and historian. They had three sons.

In 1919 Doctor Petersen joined the faculty of the University of Illinois College of Medicine. As Professor of Pathology from 1924 to 1942 he carried on extensive research, publishing—in addition to many articles in medical journals—*Protein Therapy and Nonspecific Reactions,* 1922, and with Dr. S. A. Levinson, *Skin Reactions, Blood Chemistry and Physical Status of Normal Men and Clinical Patients,* 1930. At about this time he became interested in the effect of weather and climate on disease and on the normal population. He was one of the first to investigate this field and to it devoted most of his remaining years. He published his findings in *The Patient and the Weather* (five monographs with M. E. Milliken), 1934-1938; *Lincoln-Douglas, The Weather as Destiny,* 1943; *Hippocratic Wisdom,* 1945; and *Man-Weather-Sun,* 1947. He also found time for activity in numerous medical organizations, serving as president of the Chicago Pathological and Internal Medical Societies, and as chairman of the board of the Institute of Medicine of Chicago. In addition he was active in the management of the Petersen Oven Company of Franklin Park, Illlinois, as president and later as chairman of the board.

After retiring from the University in 1942, he devoted much time to community health problems, serving on the advisory committee of the Chicago Board of Health, and helping to initiate the Chicago and Cook County Health Survey of the U. S. Public Health Service. He became interested in the problems of chronic disease, tuberculosis, alcoholism, nutrition, and conservation, serving on various committees and organizations in those fields, among them the Central Service for the Chronically Ill, the Committee for the Study of Cycles, and Provident Hospital Association. He was also Director of Clinical Research at St. Luke's Hospital for several years.

Doctor Petersen was an Honorary Fellow of The American College of Allergists. Other organizations of which he was a member are American Association for the

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News Items

SOUTHWEST ALLERGY FORUM

San Antonio, Texas, will be the meeting place for the 1951 Forum of the Southwest Allergy Forum, April 8, 9, and 10. Scientific sessions are to be held at the Plaza Hotel. The lighter side of the Forum will include a cocktail party Sunday evening, a cocktail supper and "Night in Old Mexico" at La Villita on Monday evening, and a luncheon for the ladies Monday. Allergists who are interested in presenting a paper at the Forum are urged to send the title immediately to the Secretary-Treasurer, Boen Swinny, M.D. Ideas and suggestions are also welcome.

AMERICAN ACADEMY OF PEDIATRICS—ALLERGY SECTION

At the next meeting of the American Academy of Pediatrics, Allergy Section, in Chicago, seminars on "Eczematoid Dermatoses" will be conducted on October 14 and 15 by Dr. Jerome Glaser, assisted by Dr. Norman Clein. Another seminar, on "Allergy from a Pediatric Viewpoint," will be given by Dr. James C. Overall, who will be assisted by Dr. George Logan of the Mayo Clinic.

There will be two evening panel discussions under the auspices of the Allergy Section. On October 14 at 8:00 P.M. the panel discussion will be on Eczema. Dr. Lewis Webb Hill will be the Moderator, and the panel members will be Drs. Joseph Harman Fries, Arthur J. Horesh, Samuel J. Levin, and Bret Ratner. The Moderator for the panel discussion on Respiratory Allergy October 15 at 8:00 P.M. will be Dr. Bret Ratner, and the panel members will be Drs. William P. Buffum, Susan C. Dees, Lewis Webb Hill, and Edward Scott O'Keefe.

There will also be a luncheon on October 16 sponsored by the Section on Allergy. Informal discussions will be made by Drs. Bret Ratner and Lewis Webb Hill.

PRICE REDUCTION ON CORTONE

Merck & Co., Inc., manufacturing chemists, have announced increased factory production and a reduction of almost 50 per cent in the price of Cortone, the Merck brand of Cortisone. Effective August 21, the price of Cortone to hospitals was reduced from $95 to $50 per gram. This is the fifth in a series of reductions which have, in one year, brought down the price to one quarter of the initial investigational price of $200 per gram.

Good supplies of Cortone are available to more than 6,500 hospitals which have facilities that meet certain minimum requirements. For the present the drug is to be used, during the initial period of treatment, only in patients treated in these institutions. After initial treatment the physician may provide continued treatment in his office or in the patient's home.

Dr. Herbert J. Rinkel, Kansas City, Missouri, a member of the Board of Regents of the College, presented a talk by invitation of Professor Robert Debre, Professor of the Medical Clinic for Children, before the Polyclinic of the Hospital for Sick Children in Paris on the morning of June 30 on "The Problems of Allergy in Pediatrics." Doctor Rinkel's talk was accompanied by colored slides.

BOOK REVIEWS

1949 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. Edited by Marion B. Sulzberger, M.D., and Rudolph L. Baer, M.D., Department of Dermatology and Syphilology, Post-Graduate Medical School, New York University-Bellevue Medical Center. 514 pages, 76 figures. Price $5.00. Chicago: The Year Book Publishers, 1949.

As these annual Year Books appear, they are convincing evidence of the rapid progress of our knowledge of the subject from year to year. The therapy of certain dermatoses shares the varied uses of ACTH, Cortisone (Substance E), Substance F, and other steroids derived from the adrenal gland. Considerable progress has been made in the penicillin treatment of syphilis. The demonstration of circulating specific antitreponemal antibodies is epochal. Aureomycin and chloromycetin® have proved valuable in treating obstinate dermatologic diseases such as folliculitis and sycosis, Kaposi's Varicelliform Eruption, and some forms of ulcerative stomatitis. Many forms of tuberculosis of the skin are being satisfactorily treated by streptomycin, alone or with Vitamin D_2 and/or para-aminosalicylic acid. Lawrence's studies have demonstrated regularly successful passive transfer of tuberculin-type 24-48 type sensitivity. These findings are of tremendous significance, when including 24-48 hour type sensitivity to bacterial and fungus allergens and immunologic phenomena of contact-type eczematous sensitivities.

Other important achievements are too numerous to mention here. The review of acne vulgaris and its management is complete. The allergic phase of the dermatoses is adequately presented.

The vast content makes it an outstanding daily reference. The authors' immense experience is reflected by the skill with which all topics receive their proper evaluation.

THE DIAGNOSIS OF SALMONELLA TYPES. F. Kauffmann, M.D., State Serum Institute Copenhagen, Denmark. 86 pages. Price $2.25. Springfield, Ill.: Charles C Thomas, 1950 (American Lecture Series, No. 62).

A summary of available information on the members of the genus *Salmonella* is given, which will be very useful for those who have already gained experience in the handling of the manifold problems of *Salmonella* identification. The meat of this compilation is the tabulations, which include a listing of types according to groups (196 types are recorded); an alphabetical list of types with references to the first descriptions of the more recently described types; tables on the strains to be employed for the preparation and absorption of immune sera for typing; also on cultural behavior as far as important for type identification.

CLINICAL ALLERGY. By Louis Tuft, M.D., Assistant Professor of Medicine, Temple University School of Medicine and Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital, Philadelphia. Second Edition, 690 pages, 54 figures. Price $12.00. Philadelphia: Lea & Febiger, 1949.

This timely revision of an excellent clinical first edition is very welcome. With more than a decade elapsing between the two, the accumulated new clinical and experimental data as a result of antihistamine therapy, more extensive studies of the relationship of mold fungi to allergies, aerosol therapy for respiratory allergies, the allergic basis of periarteritis nodosa, the recent experimental observations of Rich indicating that rheumatic fever may be due to an allergy, the observations of others that arthritis is allergic in nature,

the increasing importance of nervous and psychic influences, conclusive proof of atopic allergies in animals simplifying the matter of classification of allergies, and endocrine influences, all indicate the rapid development of our knowledge of syndromes due to hypersensitiveness.

However, as in the first edition, clinical procedures based upon sound observations of the author are stressed in detail.

It is replete with details compactly worded so that the new edition is invaluable as a text for the student and practicing allergist. The illustrations are excellent, the blocking of case reports is unique, and the paper stock and binding are of first quality.

PROCEEDINGS OF THE FIRST CLINICAL ACTH CONFERENCE. Edited by John R. Mote, M.D., with 52 contributors. 607 pages, numerous figures. Price $5.50. Philadelphia: The Blakiston Company, 1950.

This volume constitutes the Proceedings of the First ACTH Conference held in Chicago on October 21 and 22, 1949, under the auspices of Armour and Company. The events which led to calling the Conference are enumerated. It was finally agreed to call the Conference on behalf of all the investigators to permit exchange of information of these various investigators, who kept their studies on a broad base to ascertain the range of diseases that may be caused by endocrine defects.

Fifty-two papers are presented, together with a summary. They cover such a wide range of observations on various clinical syndromes that they cannot be enumerated here. They range from observations of ACTH on normal individuals of various ages, through its metabolic effects, its relation to other endocrines, its influence on hypertension, kidney diseases, leukemias, malignancies, rheumatoid arthritis, pulmonary infections, and the relief of allergic diseases, to its function in patients with severe personality disorders.

Of particular interest to the allergist would be the papers on "Eosinophil Observations in ACTH Therapy" by Drs. Theron G. Randolph and John P. Rollins; "The Effect of ACTH on the Clinical Syndrome of Dermatomyositis" by Dr. Charles Ragan; "Effects of ACTH in Patients with Collagen and Allied Disorders" by Dr. J. R. Elkinton and associates; "The Effect of ACTH on One Case of Periarteritis Nodosa" by Dr. Ralph Goldman and associates; "Preliminary Report on the Use of ACTH in the Hypersensitive State" by Dr. John E. Bordley and associates; "Relief of Allergic Diseases by ACTH Therapy" by Drs. Randolph and Rollins; and "Studies on the Effect of ACTH on Eosinophilia and Bronchial Asthma" by Dr. Bram Rose. It is now generally recognized that something fundamental in human physiology has been encountered, when adrenal cortical stimulation altered the clinical state of patients in widely divergent syndromes.

The editor realized that the Conference only represents the status report of the projects in progress at the time and that the results presented are not to be considered as final or conclusive. He states, "It is obvious that a tremendous amount of work will be required not only to arrive at valid conclusions concerning the effect of adrenal cortical stimulation in various disease syndromes, but, more important, to elucidate the physiologic and metabolic abnormalities which may be concerned in these various disease states."

It has been practically a year since this Conference was held, and the accumulated experience of hundreds of physicians on hospital staffs who have had ACTH available and have treated hospital patients would indicate that ACTH should soon be made available to reputable physicians who are on accredited hospital staffs, to try in their private practice. Our present stock

of information about the treatment of certain distressing syndromes with remarkable relief by the use of ACTH is rapidly taking the drug out of the experimental stage. Laboratory and clinical observations have determined quite accurately the initial and maintenance dosage of ACTH, so that any physician completely familiar with these schedules should be able to safely administer them in his private practice. He should, however, familiarize himself with any untoward reactions, avoid overdosage, and bear in mind that if a patient is carefully watched for any untoward symptoms, unfavorable reactions are reversible.

PERAZIL IN ALLERGIC RHINITIS

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SUMMARY

Perazil is another antihistaminic drug that compares more or less favorably with others available in so far as effectiveness and side effects are concerned; however, this drug appeared to us to have one outstanding quality to recommend its use; namely, longer duration of effect.

ACKNOWLEDGMENT

This study was made with technical assistance of Ellen Bachenheimer, M. T.

REFERENCES

1. Brown, E. A.; Fox, L. A.; Maher, J. P.; Nobili, C.; Norton, R. C., and Sannella, T.: A clinical evaluation of chlorcyclizine (Perazil). Ann. Allergy, 8:32-43, (Jan.-Feb.) 1950.
2. Jaros, S. H.; Castillo, J. C.; DeBeer, E. J.: The clinical application of a new piperazine compound. Ann. Allergy, 7:458-470, (July-Aug.) 1949.

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IN MEMORIAM

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Advancement of Science, American Association of Pathologists and Bacteriologists, American Society for Experimental Pathology, American Association for Physical Anthropology, American Medical Association, Illinois Medical Society, Chicago Medical Society, Chicago Medical History and German Medical Societies, American Academy of Applied Nutrition, Friends of the Land, Refugee Physicians Placement Committee, University Club of Chicago, Chicago Literary Club, and Chicago Historical Society (governing life member).

His survivors are his widow, residing at 1322 Astor Street, Chicago 10; and three sons: Edward, a resident physician at the University of Chicago; Conrad, in engineering and management with the Petersen Oven Company; and William, attending the Harvard Law School.

The officers and other members of the College extend their sincere sympathies to the family. Doctor Petersen's death is a great loss to the College because of his active participation and interest in its development and because of his pre-eminent prestige.